**Aortic Valve Replacement in Children and Young Adults: Results from a National Database**

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**ABSTRACT**
**Background:** There are several options available for aortic valve replacement (AVR), with few comparative reports in the literature. The optimal choice for AVR in each age group is not clear.
**Objectives:** Our study aims to report and compare outcomes after AVR in the young using data from a national database.
**Methods:** AVR procedures were compared after advanced matching, both in pairs and in a 3-way manner, using a Bayesian dynamic survival model.
**Results:** A total of 1,501 patients who underwent AVR in the UK between 2000 and 2012 were included. Of these, 47.8% had a Ross procedure, 37.8% a mechanical AVR, 10.9% a bioprosthesis AVR and 3.5% a homograft AVR, with Ross patients being significantly younger when compared to the other groups. Overall survival at 12 years was 94.6%. In children, the Ross procedure had a 12.7% higher event free probability (death or any reintervention) at 10 years when compared to mechanical AVR ($p = 0.05$). We also compared all procedures except the homograft in a matched population of young adults, where the bioprosthesis had the lowest event-free probability of 78.8%, followed by comparable results in mechanical AVR and Ross, with 86.3% and 89.6%, respectively. Younger age was associated with mortality and pulmonary reintervention in the Ross group and with aortic reintervention in the mechanical AVR. Out of all 3 options only the patients undergoing the Ross procedure approached the survival of the general population.
**Conclusions:** AVR in the young achieves good results, with the Ross being overall better suited for this age group, especially in children. Although freedom from aortic valve reintervention is superior after the Ross procedure, the need for homograft reinterventions is an issue to take into account. All methods have advantages and limitations, with reinterventions being an issue in the long term for all, more crucially in smaller children.

**Key words:** aortic valve disease; Ross procedure; aortic valve replacement; congenital heart disease

**Abbreviations:**
AoV – aortic valve
AVR – aortic valve replacement
B-AVR – biological heterograft
R-AVR – Ross procedure
M-AVR – mechanical valve replacement
H-AVR – homograft valve
NCHDA – National Congenital Heart Disease Audit
RVOT – right ventricle outflow tract
VSD – ventricular septal defect
HR – hazard ratio

Young patients with aortic valve (AoV) disease can be palliated by transcatheter or surgical methods but most will eventually require an aortic valve replacement (AVR). There are several options available for children and young adults: mechanical (M-AVR), pulmonary autograft or the Ross procedure (R-AVR), biological heterograft (B-AVR) and homograft valves (H-AVR). Each has its uses and limitations and, more importantly, no option is perfect. There is a set of qualities an aortic valve substitute should have, and presently there is no choice that can achieve them all, with many factors influencing the choice and long term results of an AVR. Data on outcomes vary, with few national and even fewer comparative studies. Multicenter studies would be best suited to describe and compare modern results. The objective of the current study is to describe early and long-term survival and freedom from reintervention in a national population of consecutive, unselected young patients, to compare the results of the main types of AVR in appropriately matched populations and to identify factors influencing outcome for each procedure type.

**Methods**

The National Congenital Heart Disease Audit (NCHDA) collects validated key data on cardiac procedures from all the UK units, using a mechanism for data capture, cleaning and validation similar to that for adult cardiac surgery (1).

Using linkage with census records at the Office of National Statistics (ONS), the audit database publicly reports survival rates at 30 days and 1 year following the index procedure online. Linkage with survival registries of Northern Ireland and Scotland cannot be done consistently with the patient's personal identification number, while a minority of them either have errors in their social data or are foreign. This resulted in 10.6% of patients not having data beyond 30 days, due to administrative reasons.The remaining patients have long term follow-up from either the ONS or from other entries in the database.

Indications for each operation were established by multidisciplinary teams at each center. Diagnosis and procedure codes from the European Pediatric Cardiac Code Short List are used for reporting of data. The quality index for key procedure fields is above 95%. The completeness and accuracy of non-critical data fields cannot be estimated without detailed patient-level data from each center, but there is no indication of systematic, persistent errors in reporting. The need for patient-level consent to participate in this retrospective study was waived by the National Institute for Cardiovascular Outcomes Research Board.

*Patient selection*

All available data on patients undergoing an AoV procedure for a congenital cause between April 2000 and March 2012 were selected and anonymised. Out of these, 2,767 had an AVR.

We excluded 671 patients who were >40 years old, as we considered that above this age degenerative disease is more prevalent. We also excluded those patients with associated complex heart abnormalities (n = 193), rheumatic fever (n = 15), unclassified AVR procedures (n = 313) and unknown age at index procedure (n = 74). The excluded complex heart abnormalities were: univentricular conditions, valvar atresias, interrupted aortic arch, atrioventricular septal defect, transposition of great arteries, common arterial trunk, Fallot-type defects, severe vascular abnormalities (e.g., major aorto-pulmonary collaterals) and atrial isomerism. Unclassified AVR procedures were due to errors in reporting, i.e. using a general “Aortic valve replacement” code.

Reinterventions were defined as either reoperations or catheter based procedures related to the aortic valve or root and to the pulmonary valve and right ventricle outflow tract (RVOT) for the Ross operation group. Not included were early reinterventions (within 30 days, considered connected to intraoperative events and not prosthesis durability) and aorta dilation/aneurysms repairs which were related to previous conditions (e.g., Marfan syndrome). When comparing the procedures, separate calculations were made for AoV reinterventions and any reinterventions, due to the fact that the Ross procedure is at risk of both AoV and RVOT reinterventions. This was done to ensure that the comparisons between procedures can be properly interpreted, with both AoV and overall freedom from reintervention comparisons.

*Statistical Analysis*

Frequencies are given as absolute numbers and percentages, continuous values as median (inter-quartile range). Short term mortality is calculated based on 30 day life status. Population characteristics were compared using the Mann-WhitneyU test, Kruskall Wallis test, t-test and the Fisher exact test. Estimates of long term outcomes in **Table 3** and also for neonates and H-AVR are made with the Kaplan Meier method using mortality (all cause) and reintervention, death being censoring for reintervention. Risk factor analysis for the B-AVR and H-AVR groups was performed using the log-rank test and Cox proportional hazards regression.

In addition to aggregate, non-parametric analysis of short-term and long-term survival rates, we used a Bayesian dynamic survival model to perform Variable Importance Analysis and Procedure Comparison Analysis (2). The resulting dynamic hazard ratios allowed us to differentiate early-phase and late-phase impact of variables on mortality and reintervention, providing a measure of significance for the trend in the hazard ratio, if any is present. For Procedure Comparison Analysis (2-way and 3-way), a combination of propensity score matching, restriction matching, and stochastic augmentation was used to implement matching without replacement and ensure balanced distribution of age, gender, aortic disease type, and subaortic stenosis across different procedure types (3). Separate models for mortality, AoV reintervention and overall reintervention were built, treating death and reintervention as competing, and combined using the cause-specific hazard approach to competing-risk analysis. R-AVR versus M-AVR comparison was done after matching as described above, adjusting by age, AVR type and interaction between the 2. The other comparisons are done adjusting only by AVR type. Variable importance analysis used a multivariable model including age (continous), age group, gender, aortic disease type, mitral disease, coarctation, subaortic stenosis, genetic syndrome, mitral valve procedure, coarctation repair, subaortic stenosis repair at index, with hypothetical patient profiles being used to provide context for each plot. Model coefficients are estimated using Monte Carlo Markov chain sampling of posterior distribution, and hazard ratios are plotted vs. follow-up time (dynamic hazard ratios), with corresponding, sampled-based p-values indicating their significance. Bayesian Lasso shrinkage was used as a built-in variable selection mechanism to minimize the degrees-of-freedom problem in light of increased model parameters. Missing data regarding aortic disease type were not imputed, as not enough data was available to ensure this is done properly. Instead a separate category was created ("Undetermined").

For further methodological details in the **Online Appendix**. Statistical analyses were done with STATA/IC 11.2 (StataCorp LP, College Station, Texas) and R version 3.1 (R Core Team, 2015).

**Results**

A total 1,501 patients <40 years who underwent an AVR procedure were included in the analysis. Out of these, 718 (47.8%) had R-AVR, 567 (37.8%) had M-AVR, 163 (10.9%) had B-AVR and 53 (3.5%) had H-AVR. **Table 1** shows data completeness and Table 2 demographic, clinical and procedure-related data. From the 289 patients (19.2%) with no specific data on AoV hemodynamics, 86 (29.7%) had only bicuspid morphology noted, as some centers do not systematically report aortic disease type when a bicuspid valve is seen, assuming there will be mixed aortic disease.

There were significant differences in age and gender between groups, most notably R-AVR patients being younger than in the other 3 groups (R-AVR mean age 13.7 years vs M-AVR 25.5, B-AVR 25.7 and H-AVR 18.8, p<0.001, **Figure 1**), while more males were operated using M-AVR rather B-AVR (30.9% vs 21.3%, p<0.001).

Significantly fewer patients with documented aortic regurgitation had R-AVR when compared to the rest of the group (R-AVR 23% vs 32.7% otherwise, p<0.001). No significant differences in patient distribution by lesion type were observed between the remaining 3 groups. Out of the four main associated abnormalities and corresponding concomitant procedures (**Table 2**) there were several significant differences between the R-AVR group and the remainder of the patients: subaortic stenosis had a higher frequency in the R-AVR group, with 16.2% vs 8.3% (p<0.001) as did the procedure to correct it at index, 12% vs 5.2% (p<0.001). Also, slightly fewer R-AVR patients had a VSD (4.3% vs 8.9%, p<0.001) or a VSD closure at index (0.7% vs 3.2%, p=0.001). No differences in mitral valve disease or aortic coarctation prevalence were found between groups.

The short and long term outcome estimates are shown in Table 3. The best results were achieved in the R-AVR group, with 97.3% survival and 94.7% freedom from aortic reintervention at 12 years. The H-AVR group had a poor freedom from reintervention, with 73.8% at 5 years and 59.8% at 12 years, but survival was comparable with the other 3 groups, being 93.4% at 12 years.

*Infants and children*

The majority of infants and neonates, 55/61, underwent R-AVR. Overall, the 30-day and 1 year mortality were 10.5% and 14.3%, respectively; one patient died beyond 1 year. Overall freedom from aortic reintervention is 84.7%, CI[67.9-93.2] and freedom from pulmonary valve and RVOT reintervention for the Ross operation is 72.5%, CI[52.5-85.2].

In children between 1 year and 16 years old (n=568), the 2 most-used AVR options are R-AVR (77.2%) and M-AVR (17.3%). We examined them after matching using the Procedure Comparison Analysis (**Figure 2**). Median M-AVR to R-AVR hazard ratio (HR) for death starts at 4.8 after the procedure (p=0.09, panel A) and in 10 years decreases to 2.7 (p=0.2). However, this decline is not statistically significant (p-value for difference in HR is 0.65). The difference in cumulative incidence of death between R-AVR and M-AVR is 5.1% at 10 years (M-AVR being higher, p=0.10). In terms of AoV reintervention risk, M-AVR to R-AVR HR starts at 2.8 (p=0.15) and reaches 2.6 at 10 years (p=0.08), without a significant dynamic trend (Panel B). The difference in cumulative incidence of AoV reintervention between R-AVR and M-AVR is 9.9% at 10 years (M-AVR being higher, p=0.07). When considering all reinterventions (Panel C), the M-AVR to R-AVR HR starts at 2.2 (p=0.21) and reaches 1.9 at 10 years (p=0.21), with a difference in cumulative incidence of 7.7% at 10 years (p=0.19). Finally, overall event-free probability for R-AVR is 12.7% higher than M-AVR at 10 years (p=0.05, panel D).

Ten children underwent B-AVR and 21 had H-AVR with no deaths during follow-up. In terms of AoV reintervention, 1/10 with B-AVR required a reintervention at 2.7 years (actuarial freedom from reintervention 80%), while 7/21 from the H-AVR group did (actuarial freedom from reintervention 38.4%). No other comparisons were possible between these groups and the other 2 in this age due to small sample sizes.

*Young adults*

Out of the 872 patients between 16 and 40 years old, 224 (25.7%) had R-AVR, 468 (53.7%) had M-AVR, 152 (17.4%) B-AVR and 28 (3.2%) H-AVR. All 3 main choices for AVR are used in young adults so we were able to analyze outcomes both in a 3-way comparison and also in pairs. This was necessary due to the particular overlapping pattern in age distribution (**Figure 1**), which led to different ends of this age group being matched in different comparisons (e.g. younger for R-AVR vs M-AVR, older for M-AVR vs B-AVR).

*Ross operation vs Mechanical prosthesis* vs *Bioprosthesis*: Mortality and reintervention are highest in the B-AVR group, followed by M-AVR, being lowest in the R-AVR group, with a 10-year event-free probability after matching of 78.8% (B-AVR), 86.3% (M-AVR) and 89.6% (R-AVR) respectively (**Figure 3)**.

*Ross operation vs Mechanical prosthesis (**Figure 4**):* After matching, M-AVR has a higher hazard for both death and reintervention but not statistically significant, with the exception of early mortality where HR is 3.0, p=0.09 (panels A,B,C). Overall, this does not translate into significant differences in the event free probabilities (panel D). Similar to children, we do not see significant dynamic trends for the hazard ratio.

*Ross operation vs Bioprosthesis (**Figure 5**):* In the matched group comparison, The mortality risk is significantly higher for B-AVR within the first 5 years after the index, the median HR starting at 5.4 (p=0.04) and reaching 2.5 at 10 years (p=0.12), panel A. The risk for AoV reintervention was significantly higher for the B-AVR group, with a HR starting at 2.2 early after the index, becoming statistically significant at around 1 year of follow-up and reaching 4.1 at 10 years (p=0.01), panel B. When considering overall reintervention risks, we see the same pattern (panel C), albeit with smaller HR values. These differences are reflected in the higher event free probability for the R-AVR, panel D. No significant time-dependence for death or reintervention hazard ratio was found.

*Mechanical prosthesis vs Bioprosthesis (Figure 6):* While death hazard is similar in B-AVR and M-AVR matched groups (Panel A), reintervention hazard becomes higher in B-AVR starting from 5 years after the index, with 10-year HR being 2.3 (p=0.12, Panel B). Correspondingly, cumulative incidence of reintervention is 8.8% higher in B-AVR compared to M-AVR (p=0.12, Panel D).

***Risk factors associated with AVR***

*Ross procedure:* While the risk of aortic reintervention shows no statistically-significant difference across age groups, mortality risk is higher for neonates and infants compared to children and young adults, especially within the early phase of the first 3 years of follow-up (**Figure 7A**). AoV regurgitation is associated with higher reintervention risk, compared to mixed disease and stenosis (**Figure 7B**). The risk becomes statistically significant shortly after surgery but does not exhibit a dynamic behavior. Age appears to have a steady impact on pulmonary reintervention: the younger the patient, the higher the risk (**Figure 7C**). The hazard ratios are steady and statistically significant over time. This is in contrast to the early-phase impact of age on mortality risk (**Figure 7A**). Time-independence of age hazard ratio for pulmonary reintervention suggests that the increased risk with younger age is related to the procedure performed and is not influenced by time-varying factors. We did not find gender to be a predictor of pulmonary reintervention or death.

*Mechanical prosthesis*: No predictors for mortality were found in this group. Younger age was associated with significantly higher hazard and cumulative incidence for aortic reintervention (**Figure 7D**).

*Biopsrosthesis:* Mitral valve abnormalities (HR=7.1, p=0.014, CI [1.4-35.9]) and subaortic stenosis (HR=6.3, p=0.025, CI [1.2-31.5]) were associated with higher mortality risk in this group but we were limited to univariable analysis. No predictors for mortality were found.

*Homograft:* A total of 3/53 patients died in this group, 2 of them also being the only 2 neonates operated with a homograft AVR, pointing to age under 30 days being a risk factor. Younger age was also identified as a risk for aortic reintervention (univariate analysis HR=1.08/year, p=0.02, CI [1.01-1.15]).

*Comparison with the matched general population*

Survival after R-AVR, B-AVR and M-AVR was compared with that of the general population, with R-AVR being the only method having a survival pattern closely similar to that of the general population. The method, results and discussions are available (Online Appendix).

**Discussion**

This study shows that the prevalence of various AVR options is in keeping with what is known and expected in children and young adults (**Central Illustration**). The Ross procedure is the most common option in children due to its growth potential but its utilization decreases in young adults. All valves achieved good survival, the lowest 12-year estimate being for M-AVR at 90.6%. The 12-year freedom from reintervention is over 90% for R-AVR and M-AVR but only 75% and 59.5% for B-AVR and H-AVR respectively (**Table 3**).

More insight was gained by detailed subgroup analyses, in which R-AVR emerged as overall superior, at worst comparable to M-AVR in young adults. In a separate analysis examining UK trends we found that the Ross procedure has excellent results in young patients but, curiously, its usage is gradually decreasing over time, the main competitors being balloon valvoplasty in children and M-AVR in young adults (4).

Most of the data available on long term outcomes in AVR in children and young adults comes from single center studies, with just a few multicenter reports and even fewer comparative ones. The German-Dutch registry reports excellent results with the Ross procedure in older patients (5), while the Society of Thoracic Surgeons reports short term results from a national database in infants (6). Published data on outcomes after each individual AVR type is readily available, but patient age, clinical status, and methodology vary widely. Comparative studies in the young are scarce and confronted with the same limitations we encountered, specifically differences in patient characteristics. No randomized AVR studies were performed in children and only a few were done in adults. A review of modern literature on AVR in the young shows a particular interest in the Ross procedure, in some reports survival being comparable with that of the general adult population (7-9). Careful patient selection and technical modifications are most likely responsible for the improved results (5,9,10). This naturally leads to the question: is the Ross procedure the gold standard in AVR in the young? And if so, where do we stand in regards to the other 3 options?

*Neonates and infants*

In our study the majority of them  underwent R-AVR. But the Ross operation is not always seen as first choice for small children. Surgical or transcather repair are sometimes preferred to postpone AVR, on the grounds that palliation can achieve good results (11,12), while AVR mortality in these patients is high, ranging from 15-50% (12-14). We have seen a lower early mortality in this age group (10%) but still we found that age under 1 year is a risk factor in the R-AVR overall. The lower mortality may be related to excluding patients with complex associated defects, like interrupted arch, specifically found to be a risk factor by others.(6, 15) Hickey et al report high mortality in neonates and infants undergoing a Ross procedure, but these patients had either critical stenosis or a failed previous repair, the results being otherwise acceptable for patients older than 3 months presenting electively (10). In other words performing a Ross procedure in unfavorable circumstances may lead to unfavorable results, but these are situations where alternatives are limited.

We found that age<1 year was a significant risk factor for pulmonary conduit reintervention, as previously reported, in keeping with the notion that a small conduit is rapidly outgrown (5). Examining the best treatment sequence in small children (including palliation by valve repair and balloon dilation) was beyond the scope of this paper, but the small number of AVRs in infants nationally suggests this option is considered after all other treatment paths are exhausted.

*Children*

It has previously been shown that hetero- and homografts are not suitable in the long term in the pediatric population and should be used with caution. Bioprosthesis valves have been associated with a risk of rapid deterioration and explantation (16), or even catastrophic early failure (17). Results achieved with homograft valves have been variable, but a high incidence of reoperation has been reported (16,18). This was mirrored in our group by the majority of children reiceiving either a Ross autograft or a mechanical valve. Compared to R-AVR, M-AVR has higher mortality, especially in the early phase, and slightly higher aortic reintervention risks. Taking into consideration the RVOT reinterventions, it results in a 12.7% difference in event-free probability at 10 years in favour of the Ross (**Figure 2**). Alsoufi et al. also found a significantly higher mortality risk after M-AVR, but a higher risk of aortic reintervention in the Ross group, noting that patients with rheumatic disease were included and found to be at increased risk for reintervention (19). Ruzmetov reported a single center series with similar results as our national audit (16). In a study with 10 years of follow-up Lupinetti also found that mechanical AVR in children had worse results when compared to autograft/allograft (20).

*Young adults*

In young adults, all main 3 choices of valves are available, patients receiving a Ross autograft being the youngest in our group, those having a mechanical AVR the oldest, with the bioprosthetic in between (**Figure 1**). In a 3-way matched comparison, we found that biological valves are associated with the worst results, followed by mechanical valves and Ross with comparable results, albeit slightly better for the latter (**Figure 3**). These results persist in pairwise comparisons, which broaden the matched groups depending on the particular overlap in age (**Figures 4-6**).

Comparing the Ross procedure and mechanical AVR we found a slightly higher mortality and aortic reintervention risk in M-AVR, but overall event free probabilities are comparable after considering the RVOT reinterventions (**Figure 4**). Mokhles compared the R-AVR and optimally anticoagulated M-AVR in propensity score matched groups for the non-elderly adult population, finding no differences in mortality and significantly higher aortic reintervention rates in the Ross group (21). There are several differences between this study and ours: our patients are younger, we did not use propensity matching but rather a composite approach, and finally our M-AVR patients were not under highly specialized anticoagulation but under real life conditions when compliance is variable.

Few reports compare the Ross procedure with the bioprosthetic valve in the young. Ruzmetov reported better survival with Ross at 15 years (91% vs 84%) (but children were also included and noted to have higher mortality), comparable freedom from aortic reintervention, and higher risk of AoV explantation in the bioprosthesis group (22). We found no differences in long term mortality in our matched groups (the difference being we compared only young adults), but we did find a higher risk for AoV reintervention in the B-AVR group, especially starting after 2 years of follow-up (**Figure 5**).

Comparing the mechanical to bioprosthetic valves in matched young adults groups, we found modest differences in mortality and aortic reintervention, the risks being slighly higher in the latter (**Figure 6**). Ruel examined mechanical prostheses with biological (heterograft and homograft) in a population of young adults and found comparable results in long term mortality but significantly worse freedom from reintervention in the biological valve group (worse in the heterograft vs homograft). In addition there was a lower overall quality of life in the mechanical group (23). Interestingly, when patients of similar ages are compared in our study, the differences are not as striking as previosly reported, but this might also be due to the small sample size. The results suggest that B-AVR remains a reasonable option for young adults, particularly in keen patients such as women contemplating pregnancy.

*Risk factors associated with AVR*

Our data originated in a procedure-based audit, therefore we had few other variables to consider as predictors. The focus became age, valve disease type and concomitant defects and procedures, also looking into the dynamic effect they might have during follow-up. The choice to apply dynamic survival analysis was influenced by the belief that some key drivers of outcome may not have the same impact in various stages of follow-up. Our results highlighted 3 cases of age influencing outcome: mortality risk and pulmonary reintervention for the Ross procedure, and aortic reintervention for M-AVR (**Figure 7**). In the first case, we saw a strong early-phase hazard for neonates and infants compared to children and young adults, consistent with the more severe clinical condition associated with presentation at earlier ages. In the other 2 cases, an increased hazard for younger patients was noted which lasted long into follow-up. This is consistent with an inherently higher risk due to the initial surgery. A dynamic model allowed us to differentiate these 2 patterns and hypothesize about the different root-causes of each. Of course an alternative is to build independent models for different age groups to allow for arbitrary hazard ratios between them, but this would not be as efficient a use of data as building a single model that contains all age groups.

In summary, the U.K. national dataset allowed complete procedural and survival follow up for AVR carried out in the young. The Ross procedure has multiple advantages which seem to extend beyond childhood, being superior to other AVR types when compared in matched groups, especially in children, but all prostheses perform reasonably well overall. The study is limited by absence of more clinical data such as operative timing and echocardiography, also by relatively short follow-up. Future planned research revolves around linkage with other UK valve registries to obtain longer follow up as well as examining the role of surgical and balloon valvoplasty in delaying AVR. Cost and quality of life analyses would similarly add to the quest for finding the most advantageous valve substitutes for individual patients.

**Perspectives**

*Competency in Patient Care and Procedural Skills:* While most methods of aortic valve replacement in children and young adults are associated with good outcomes, the Ross procedure achieves better survival than other valve replacement options, but is associated with more frequent need for subsequent interventions.

*Translational Outlook:* Longer follow-up studies may identify high and low-risk subgroups and better inform selection of optimum approaches for individual patients.

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## FIGURE LEGENDS

**Central Illustration: Aortic valve replacement and the Ross operation in children and young adults**. Dynamic changes of risk of mortality or reintervention during follow up period after AVR operation by the procedure types and the age groups. Risk of both mortality and reintervention decrease with the patient age and increase during follow-up. The overall increase of risk differs depending on the AVR procedure type and the speed of increase in risk during the various stages of follow up time is not proportional across the AVR types. Distances and the levels of increase in risk are drawn schematically and, therefore, are not precise.

**Figure 1**: **Age distribution histogram by procedure type.** Columns represent fraction from total for 1 year wide bins. Continous line represents the kernel density.

**Figure 2**: **Comparison of long term outcomes between Ross AVR and mechanical AVR in children using matched groups**. Hazard functions (top row) and dynamic hazard ratios/event free probability differences (bottom row with confidence intervals) are shown, derived from a Bayesian Mixture Survival Model using the additive mixture of 2 Weibull hazards. Samples are matched by gender, age, aortic disease type, association of subaortic stenosis, using a stochastic algorithm with propensity score matching. The model was adjusted by age group and the interaction between age group and AVR type was included.

**Figure 3**: **Comparison of long term outcomes between the Ross operation, mechanical AVR and bioprosthesis for young adults (16-40 years old).** Confidence bands are not included to avoid clutter. These are unadjusted event curves after matching using a 3-way composite algorithm (described in methods).

**Figure 4: Comparison of long term outcomes between Ross AVR and mechanical AVR in young adults using matched groups.** See caption of Figure 2 for details on panel rows, model and matching. The model is unadjusted.

**Figure 5**: **Comparison of long term outcomes between the Ross operation and bioprosthesis AVR in young adults using matched groups.** See caption of Figure 2 for details on panel rows, model and matching. The model is unadjusted.

**Figure 6**: **Comparison of the mechanical AVR and biopsothesis in young adults in terms of long term outcomes in matched groups.** See caption of Figure 2 for details on panel rows, model and matching. The model is unadjusted.

**Figure 7**: **Risk factors for death or reintervention in Ross and Mechanical AVR.** Hazard functions are derived from multivariable bayesian mixture survival models (separate for Ross and mechanical AVR), using the additive mixture of 2 Weibull hazards, adjusted by age (continous), age group, gender, aortic disease type, mitral disease, coarctation, subaortic stenosis, genetic syndrome, mitral valve procedure, coarctation repair, subaortic stenosis repair at index. The mid-point of each age group was chosen as the age of its corresponding hypothetical patient, while the rest of the categorical variables were set as zero. **Panel A:** Impact of age on mortality risk for Ross procedure. **Panel B:** Impact of aortic disease type on reintervention risk for Ross procedure. **Panel C:** Impact of age on risk of pulmonary reintervention for Ross procedure. **Panel D:** Impact of age on reintervention risk for the Mechanical AVR procedure in young adults.

Dynamic hazard ratios, CI differences, event free probability differences and their corresponding p values can be seen in the Online Appendix

**Table 1. Data Completeness**

| | |
|---|---|
| National Health System ID | 100% |
| Aortic Valve Hemodynamics | 80.7% |
| Diagnosis | 97.9% |
| Weight | 92.8% |
| Sternotomy number | 79.8% |
| Hospitalization period | 97.5% |
| Discharge status | 99.9% |
| 30 day status | 89.3% |

**Table 2. Patients characteristics and procedure data by aortic valve replacement (AVR) type**

| | Total | Ross autograft | Mechanical AVR | Bioprosthetic AVR | Homograft AVR |
|---|---|---|---|---|---|
| Patients (n) | 1501 | 718 | 567 | 163 | 53 |
| Age (y) | | | | | |
| Median (IQR) | 17.8 (12.1-28.7) | 13.1 (7.5-17.0) | 26.3 (17.6-33.6) | 24.8 (20.1-31.0) | 16.4 (12.0-27.6) |
| Gender (n, %) | | | | | |
| Male | 1091 (72.7) | 514 (71.6) | 446 (78.7) | 104 (63.8) | 27 (51.0) |
| Age group (n, %) | | | | | |
| Neonate (<30 days) | 8 (0.5) | 6 (0.9) | 0 (0) | 0 (0) | 2 (3.8) |
| Infant (1-12 months) | 53 (3.5) | 49 (6.8) | 1 (0.2) | 1 (0.6) | 2 (3.8) |
| Child (1-16 years) | 568 (37.9) | 439 (61.1) | 98 (17.3) | 10 (6.1) | 21 (39.6) |
| Young adult (16-40 years) | 872 (58.1) | 224 (31.2) | 468 (82.5) | 152 (93.3) | 28 (52.8) |
| Follow-up (y) | | | | | |
| Median (IQR) | 5.3 (2.1-8.6) | 6.6 (2.5-9.6) | 4.7 (1.8-7.5) | 3.5 (2.0-5.6) | 5.6 (1.1-8.5) |
| Aortic valve disease, (n, %) | | | | | |

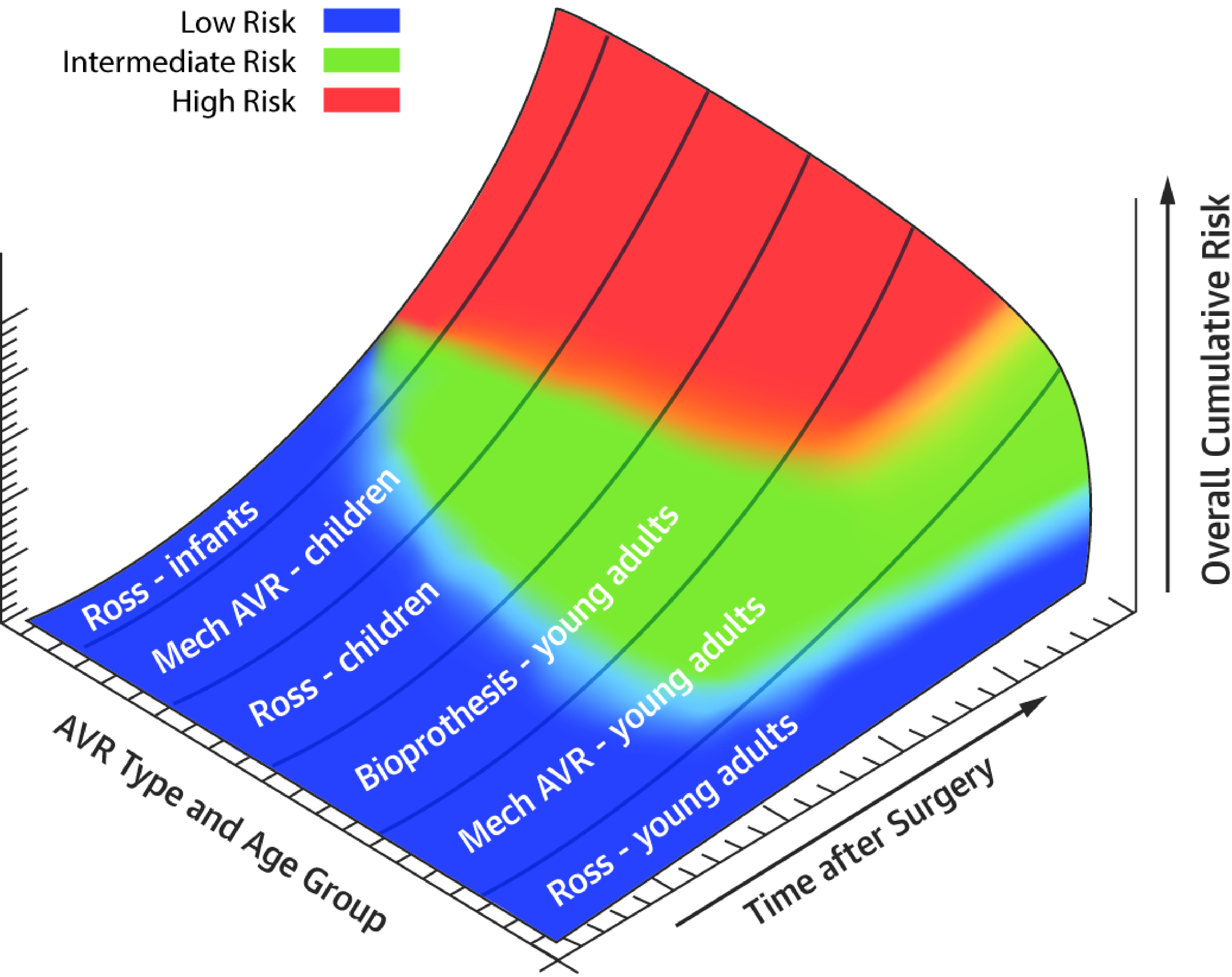
| | | | | | |
|---|---|---|---|---|---|
| Stenosis | 492 (32.8) | 268 (37.3) | 148 (26.1) | 25 (15.3) | 8 (15.1) |
| Regurgitation | 421 (28.0) | 165 (23.0) | 181 (31.9) | 58 (35.6) | 17 (32.1) |
| Mixed | 299 (19.9) | 190 (26.5) | 76 (13.4) | 59 (36.2) | 17 (32.1) |
| Unkown | 289 (19.3) | 95 (13.2) | 162 (28.6) | 21 (12.9) | 11 (20.7) |
| Marfan Syndrome (n, %) | 41 (2.7) | 0 (0) | 37 (6.5) | 1 (0.6) | 3(5.7) |
| Concomitant procedures | | | | | |
| Mitral valve | 58 (3.9) | 22 (3.1) | 29 (5.1) | 5 (3.1) | 2 (3.8) |
| Subaortic | 127 (8.5) | 86 (12.0) | 32 (5.6) | 5 (3.1) | 4 (7.5) |
| Ventricular septal defect repair | 30 (2.0) | 5 (0.7) | 15 (2.6) | 7 (4.3) | 3. (5.7) |
| Coarctation/Hypoplasia repair | 18 (1.2) | 7 (1.0) | 8 (1.4) | 3 (1.8) | 0 (0) |

**Table 3. Survival and freedom from reintervention by aortic valve repair (AVR) type**

| | Overall | Ross procedure | Mechanical AVR | Bioprosthetic AVR | Homograft AVR |
|---|---|---|---|---|---|
| Patients | n=1501 | n=718 | n=567 | n=163 | n=53 |
| Survival (%) | | | | | |
| 30-day | 98.4 | 98.9 | 98.0 | 97.4 | 97.9 |
| 5 years estimate [95% CI] | 96.2 [95.0-97.2] | 97.6 [96.0-98.6] | 95.0 [92.4-96.7] | 94.9 [89.3-97.6] | 93.4 [81.0-97.8] |
| 12 years estimate [95% CI] | 94.6 [92.8-95.9] | 97.3 [95.6-98.4] | 90.6 [85.8-93.9] | 92.6 [84.2-96.7] | 93.4 [81.0-97.8] |
| Freedom from aortic reintervention (%) | | | | | |
| 5 years estimate [95% CI] | 96.0 [94.6-97.0] | 97.2 [95.5-98.3] | 96.2 [93.7-97.6] | 94.3 [86.0-97.7] | 73.8 [55.3-85.6] |
| 12 years estimate [95% CI] | 90.4 [87.1-93.0] | 94.7 [91.7-96.6] | 91.8 [86.8-94.9] | 75.0 [53.2-87.8] | 59.5 [37.9-75.7] |
| Freedom from pulmonary valve reintervention (%) | | | | | |
| 5 years estimate [95% CI] | | 98.0 [96.4-98.9] | | | |

| | |
|---|---|
| 12 years estimate [95% CI] | 91.1 [87.3-93.8] |

Unadjusted Kaplan Meier estimated values with death and reintervention (aortic and pulmonary) as failures; death is censoring for reintervention.


Low Risk
Intermediate Risk
High Risk
Overall Cumulative Risk
Ross - infants
Mech AVR - children
Ross - children
Bioprothesis - young adults
Mech AVR - young adults
Ross - young adults
AVR Type and Age Group
Time after Surgery

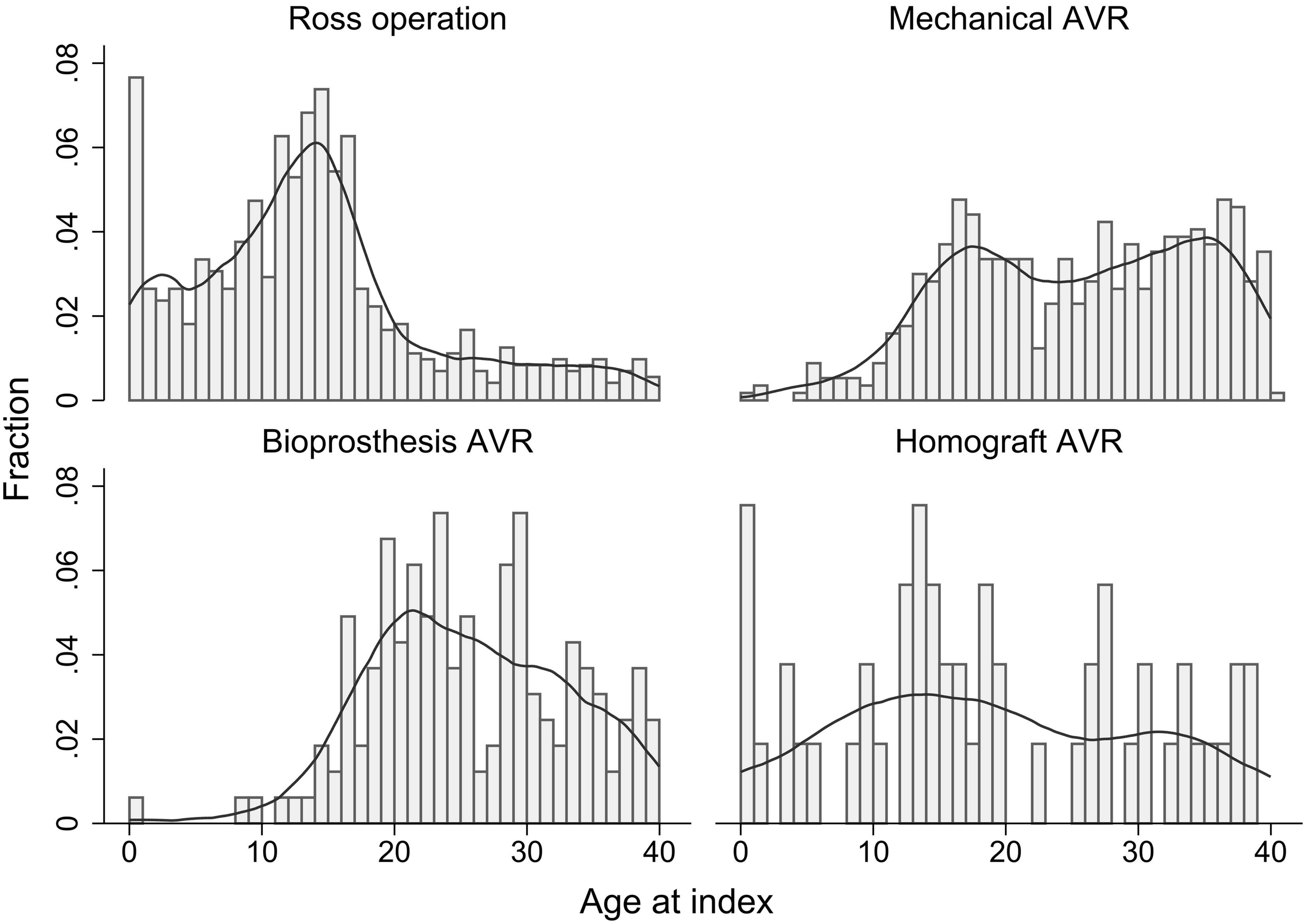
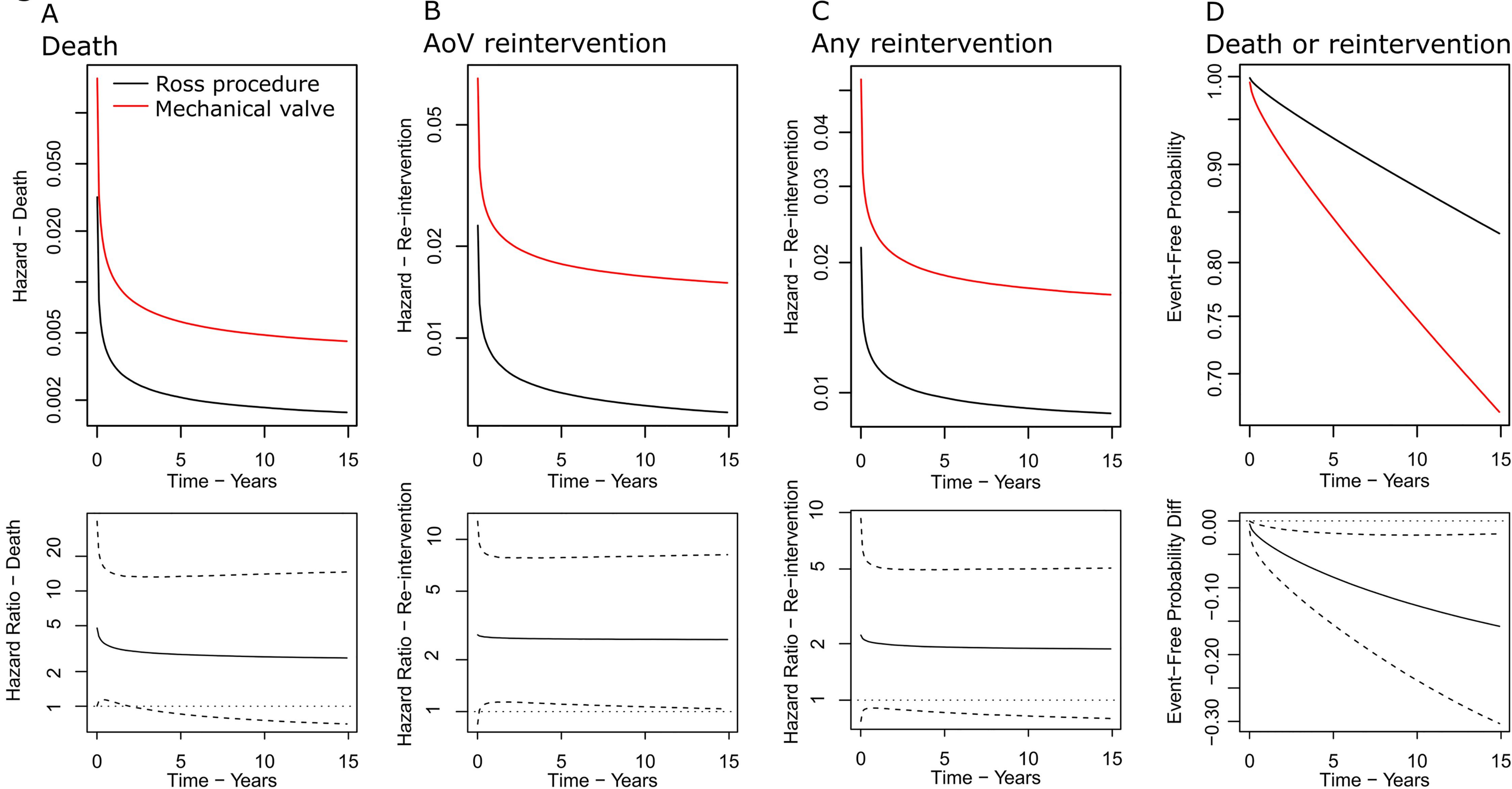
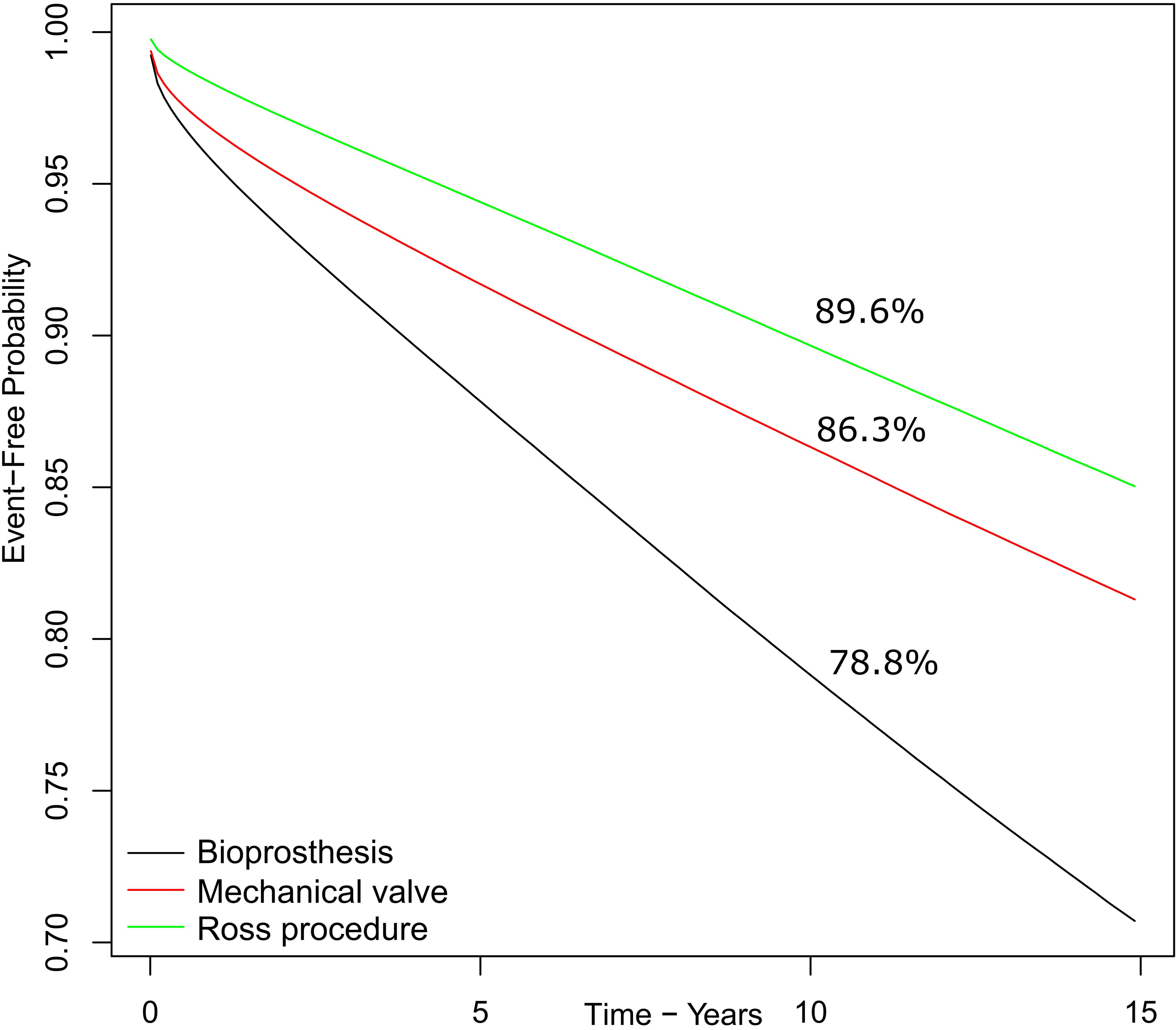

Ross operation
Mechanical AVR
Bioprosthesis AVR
Homograft AVR
Fraction
0
.02
.04
.06
.08
0
10
20
30
40
Age at index

Figure 2



A
Death
Ross procedure
Mechanical valve
Hazard − Death
0.002
0.005
0.020
0.050
Time − Years
0
5
10
15
B
AoV reintervention
Hazard − Re−intervention
0.01
0.02
0.05
C
Any reintervention
0.01
0.02
0.03
0.04
D
Death or reintervention
Event−Free Probability
0.70
0.75
0.80
0.90
1.00
Hazard Ratio − Death
1
2
5
10
20
Hazard Ratio − Re−intervention
1
2
5
10
Event−Free Probability Diff
−0.30
−0.20
−0.10
0.00

Figure 3



1.00
0.95
0.90
0.85
0.80
0.75
0.70
Event−Free Probability
89.6%
86.3%
78.8%
Bioprosthesis
Mechanical valve
Ross procedure
0
5
10
15
Time − Years

Figure 4

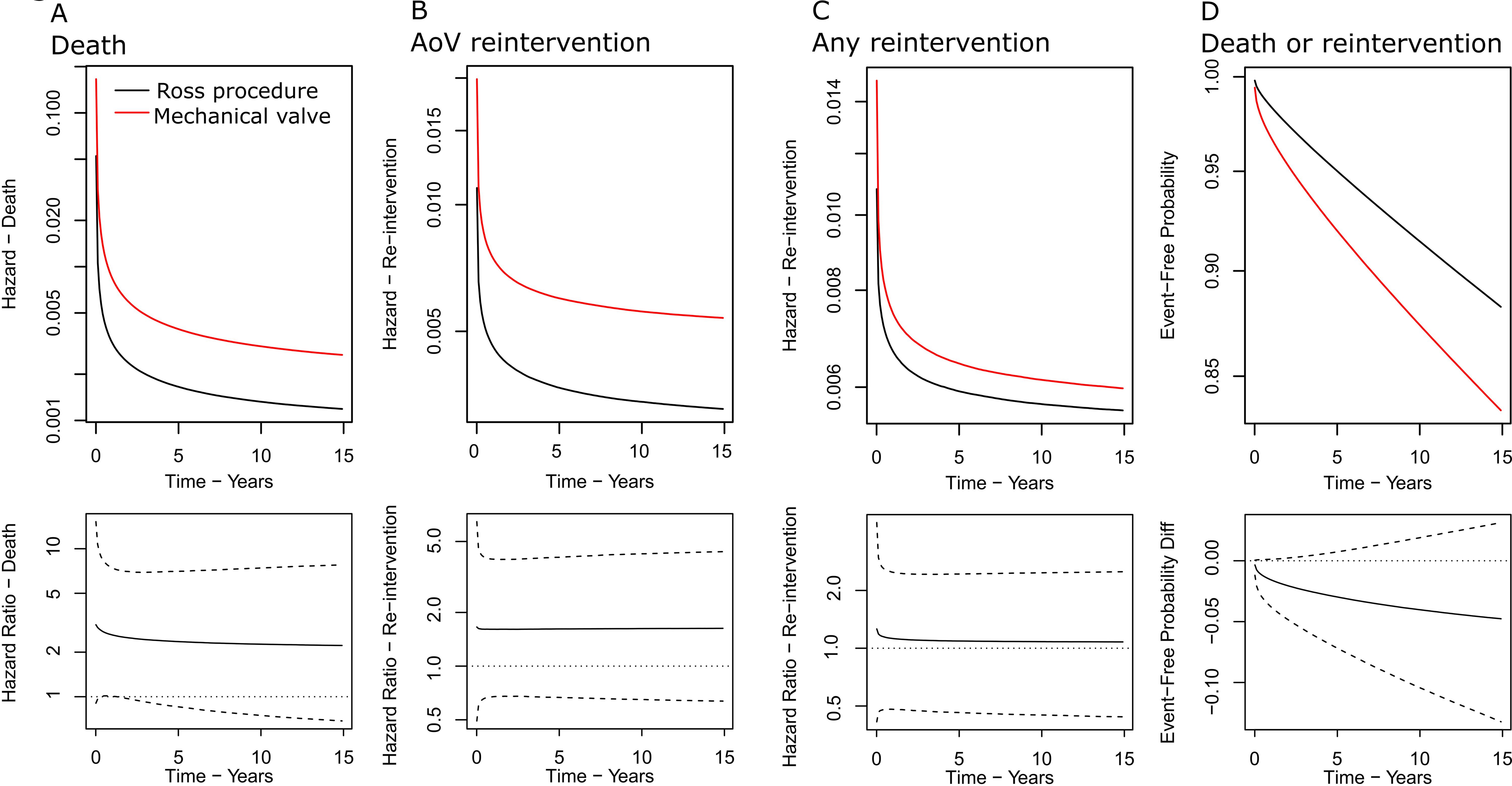
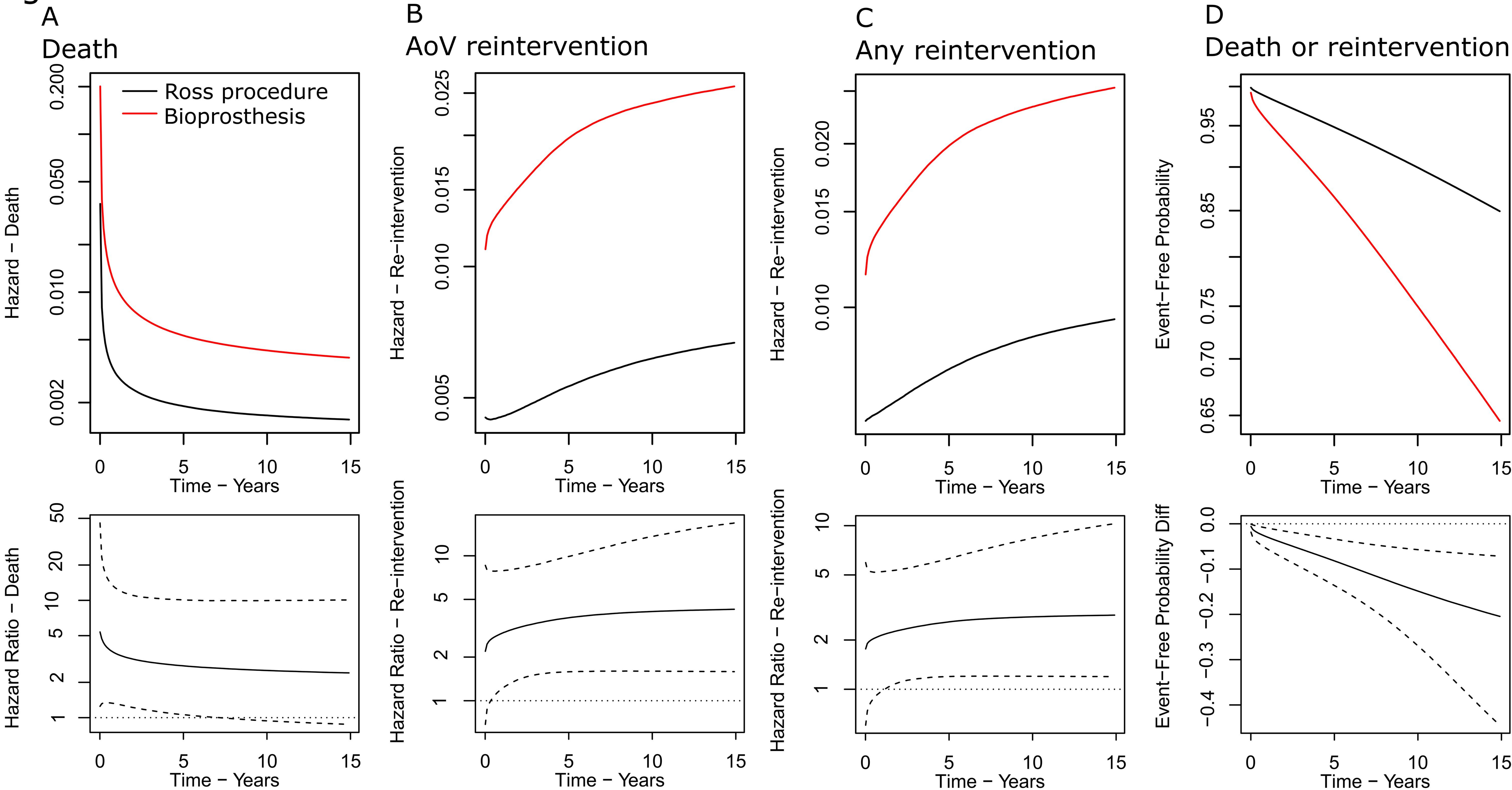
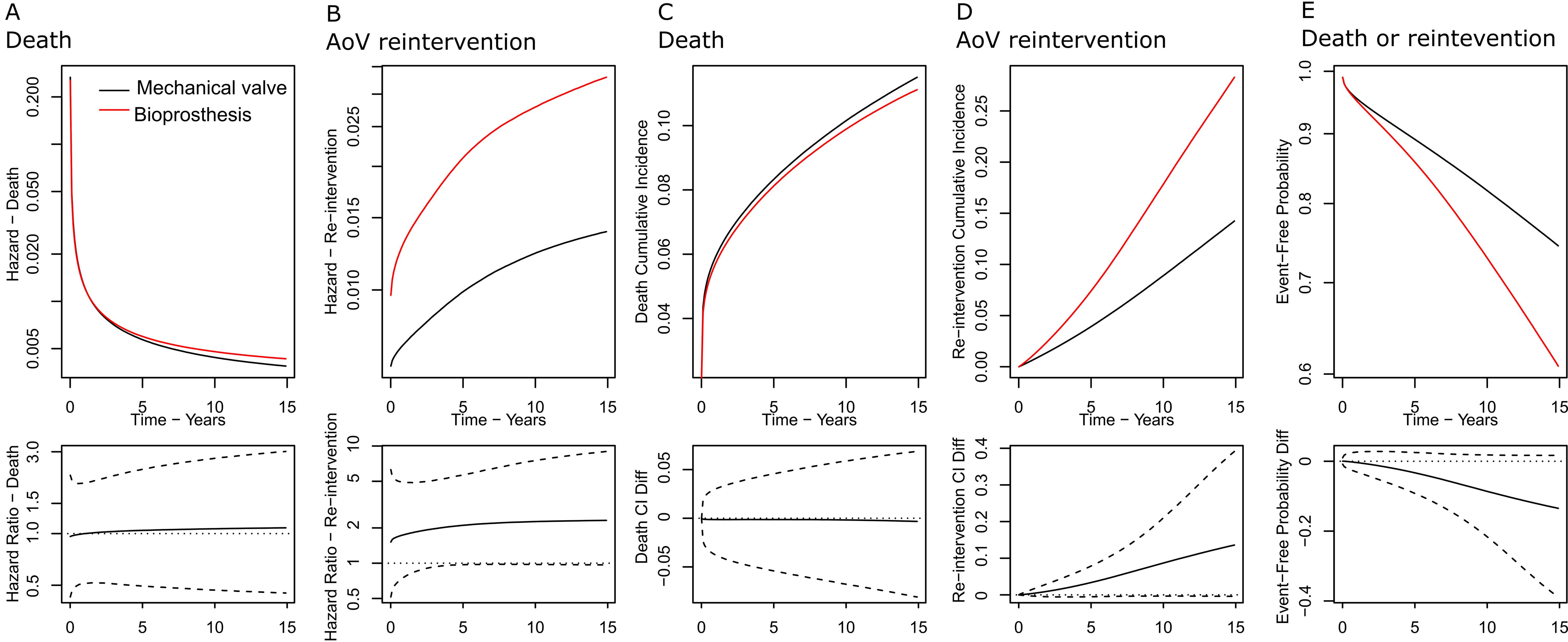

A
Death
Ross procedure
Mechanical valve
Hazard − Death
0.001
0.005
0.020
0.100
Time − Years
Hazard Ratio − Death
B
AoV reintervention
Hazard − Re−intervention
0.005
0.010
0.015
Hazard Ratio − Re−intervention
0.5
1.0
2.0
5.0
C
Any reintervention
0.006
0.008
0.010
0.014
D
Death or reintervention
Event−Free Probability
0.85
0.90
0.95
1.00
Event−Free Probability Diff
−0.10
−0.05
0.00
0
5
10
15
1
2
10

Figure 5



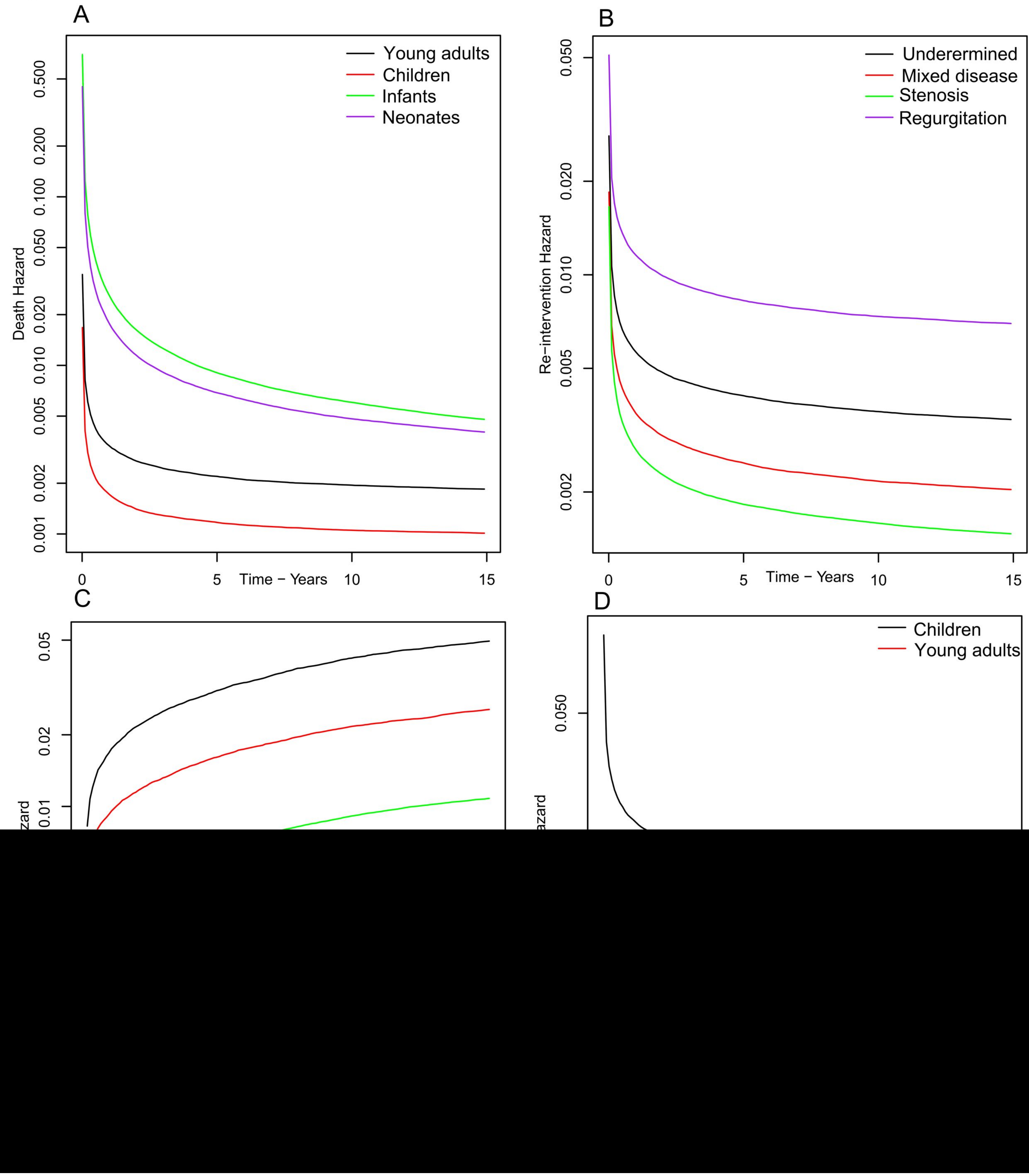
A
Death
Ross procedure
Bioprosthesis
Hazard − Death
0.200
0.050
0.010
0.002
Time − Years
Hazard Ratio − Death
50
20
10
5
2
1
B
AoV reintervention
Hazard − Re−intervention
0.025
0.015
0.010
0.005
Hazard Ratio − Re−intervention
10
5
2
1
C
Any reintervention
0.020
0.015
0.010
D
Death or reintervention
Event−Free Probability
0.95
0.85
0.75
0.70
0.65
Event−Free Probability Diff
0.0
−0.1
−0.2
−0.3
−0.4
0
5
10
15

# Figure 6



A
Death
Mechanical valve
Bioprosthesis
Hazard − Death
Time − Years
Hazard Ratio − Death
B
AoV reintervention
Hazard − Re−intervention
Time − Years
Hazard Ratio − Re−intervention
C
Death
Death Cumulative Incidence
Time − Years
Death CI Diff
D
AoV reintervention
Re−intervention Cumulative Incidence
Time − Years
Re−intervention CI Diff
E
Death or reintevention
Event−Free Probability
Time − Years
Event−Free Probability Diff

Figure 7

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**APPENDIX A: Methodological Details**

In this section, we provide methodological details pertaining to various steps in the data preparation and analysis.

**Statistical Matching**

For Procedure Comparison Analysis, we used a custom matching algorithm to ensure a balanced distribution of gender, age, aortic disease type, and subaortic stenosis across observations for different procedures. This algorithm relaxed a requirement in common matching algorithms such as Propensity Score Matching, that the matched dataset must contain an equal number of observations from each treatment group. This requirement would lead to two equally-undesirable outcomes: small matched datasets or repeated observations. The first outcome is especially unattractive since our dataset is relatively small, and our dynamic survival model doubles the number of degrees of freedom used in the model. The second outcome is also unfavorable because duplicate observations can invalidate the outcome of a cross-validation-based approach for selecting the shrinkage parameters in the survival model. A second shortcoming of the existing matching algorithms is that they deterministically select a fixed subset of the observations in the matched data set; in other words, certain observations are never used in the remainder of the analysis. Again, given the small number of observations in our problem, we viewed this shortcoming as a critical one.

The matching algorithm constructs and combines 2-D histograms of gender and age for each treatment group into a target profile, scaled up or down for each treatment to maximize sample size while retaining relative contribution from each histogram cell. Random sub-sampling of observations within each cell is followed by application of t-test or chi-squared test to ensure balanced distribution of age and gender in matched sets. We considered Kolmogorov-Smirnov test (KS), which assesses balance of two distributions not just in terms of their mean, as in t-test. However, we preferred t-test and chi-squared test for two reasons: First, KS's generalization to multiple distributions is not a fully-established subject. Secondly, in the context of regression modeling, the more detailed matching achieved by KS is unnecessary and can lead to excessively small matched data sets. To ensure balance with regards to aortic disease type and subaortic stenosis, we applied similar tests to each output of the algorithm and accept only those that pass the test. We set a threshold of 0.25 for the p-value of all statistical tests in this paper, although actual p-value for matched datasets was generally much higher.

**Bayesian Dynamic Survival Model**

We used the R package BayesMixSurv – co-developed by two of the authors of this paper – to analyze the data. This package builds a Bayesian dynamic survival model with Lasso shrinkage (using Laplace prior on coefficients of each component), using an additive mixture of two hazard functions, each of which corresponds to a Weibull distribution for the event density function with a different shape parameter. While each hazard component consists of the usual product of a baseline hazard function and the exponential regression component, total hazard does not lead to a proportional hazard model. As such, hazard ratio for a variable is both time dependent and 'context-dependent'. In other words, the incremental hazard due to a change in the value of a variable depends not only on time, but also on the value of other variables. In our case, context-dependence was weak due to the presence of few statistically-significant variables. Yet, when in using BayesMixSurv we must always report the context variables when discussing the hazard ratio for a focus variable.

Model estimation as well as prediction is done in a Bayesian framework, using Monte Carlo Markov Chain sampling of posterior distribution with a univariate slice sampler embedded in a Gibbs sampling framework. Shrinkage parameters are tuned via maximization of model log-likelihood in a 5-fold cross-validation setting. Lasso shrinkage tends to push the coefficients of many variables towards zero, thus playing the role of a built-in variable selection algorithm. This is important since it allows us to avoid splitting the data for variable selection and model estimation, given the small data set and few events available.

**Sampled-Based Prediction and Analysis**

Since BayesMixSurv is a dynamic model, the hazard ratio for a given variable is not only time-dependent, but also 'context-dependent'. Time-dependence means that the hazard ratio changes with time, while context-dependence means it changes with values of other variables used in the model. In our analysis, since few variables were discovered to have significant impact on outcome, context-dependence was of little impact. Nevertheless, all results must be viewed in the context of values assumed for other variables. We therefore used a 'hypothetical patient' with fixed values of all covariates (except variable whose hazard ratio is being studied) when generating our plots. Unless explicitly specified otherwise, this hypothetical patient had the following profile (values chosen to best represent the original data set): male gender, age of 19.6 years, mixed aortic disease type, all other disease indexes: 0.

**Competing-Risk Approach**

Death is considered censoring for reintervention and vice versa. Treating reintervention as censoring for death is driven by our belief that reintervention is a sufficiently important event that it can significantly alter the mortality risk after its occurrence. We use the cause-specific hazard approach to competing-risk analysis, where independent models for each cause (death and reintervention here) are built, and then combined together[1].

**Procedure Comparison Analysis**

In the first group of BayesMixSurv models, we study the impact of procedure type on mortality and reintervention risk. Since we used matched data sets for this analysis, which are smaller than the original data, and after the Variable Importance Analysis suggested that age is the only significant variable, we decided to perform Procedure Comparison Analysis focused on a reduced set of variables. For comparing the Ross procedure and Mechanical AVR, we included data for two age groups, children and young adults. In this model, in addition to using procedure type as a binary variable (Ross/Mech), we also included age group (binary variable) as well as its interaction with procedure type. As an alternative to this full interaction within a single model, we could have created two independent models for each age group, and the results would be very similar. For pairwise comparison of Bioprosthesis to Ross operation or Mechanical AVR, data availability forced us to focus only on young adults, and the models included a binary procedure type variable only. Similarly, for three-way comparison of Ross/Mech/Bio we focused on young adults, using the output of a three-way version of our custom matching algorithm. In all cases, we used 100 instances of the stochastic matching algorithm to build BayesMixSurv models, and combined the predictions from all 100 trained models to produce a final set of predictions. A sampling-based approach to estimation and prediction allowed us to perform the combination with ease and produce meaningful confidence intervals for the aggregate results.

**Variable Importance Analysis**

This set of analyses used the original data set of 1,501 observations. We focused on the Ross and Mechanical AVR for this analysis, given the small size of data and few events for Bioprosthesis and Homograft. For the Ross operation, we used the full data set containing all 4 age groups, while for Mechanical AVR we focused on children and young adults only, since there were 0 and 1 observations in neonate and infant category for this category. Again, the sampling-based approach facilitated this final blending stage. No matching was necessary for this set of analyses, since each model was focused only on one procedure type.

**Survival comparison with the general population**

We compared the UK population-based survival curve with the survival of our patients. To do this, we developed an R script to extract mortality probabilities from the life tables of Office of National Statistics[2] for each patient given their age and gender. Subsequently, we run 1000 times Monte Carlo (MC) simulations[3] to estimate the expected survival of each patient in general population. Simulations started from the year of operation and advanced in yearly increments. Simulated patient-level events were then aggregated to form Kaplan Meier curve which represented the baseline expected survival of the group of patients if they did not have the disease and had come from the UK general population.

**REFRENCES**


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2. Office for National Statistics. National Life Tables, United Kingdom, 1980-82 to 2011-13. London, England: Crown Publications 2014.
3. Robert CP, Casella G. Monte Carlo Statistical Methods. Springer Texts in

Statistics. 2004.

**APPENDIX B – comparison with the general population, results and discussion**

Survival for both children and young adults was significantly higher in the simulated group of healthy individuals when compared to both types of prostheses, being higher than 99% at 10 years. Results in the Ross group are similar for both age groups, and closest to that of the general population (98.3% vs 99.8% for children and 98.5% vs 99.5% for young adults respectively, p<0.001,). M-AVR does not achieve comparable survival with the general population in either age group (90.6% vs 99.8% in children and 90.5% vs 99.5% in young adults, p<0.001) and neither does B-AVR (90.2% vs 99.7% in children and 92.4% vs 99.5% in young adults, p<0.001).

The main goal of the national audit is to ensure that results in all centers in the UK are both good and uniform. When looking at the most common AVR procedures, they do not achieve survival similar to that of the general population, as 10-year mortality is very low in the healthy young (less than 1%), while being little over 1.5% after the Ross operation, 8.5% after the biological AVR and approximately 10% after the mechanical AVR. These results underline the need for adjusted expectations for each age group, as achieving the same survival after AVR in the young as in healthy individuals is an unreasonable goal, at least at present. The fact that the Ross procedure overall closely approaches this goal, while other valve replacement types do not, makes it a viable and even desirable option, especially in the young.

## APPENDIX C

Plots detailing the impact of the age group in mortality and reintervention for the Ross procedure, showing hazard, cumulative incidence and event free probability for all four groups (Figure 1) and hazard ratio and cumulative incidence difference with their estimated p values in two-by-two comparisons (Figures 2-7). Age groups are as follows: 1 – neonates, 2 – infants, 3 – children, 4 – young adults.

Figure 1

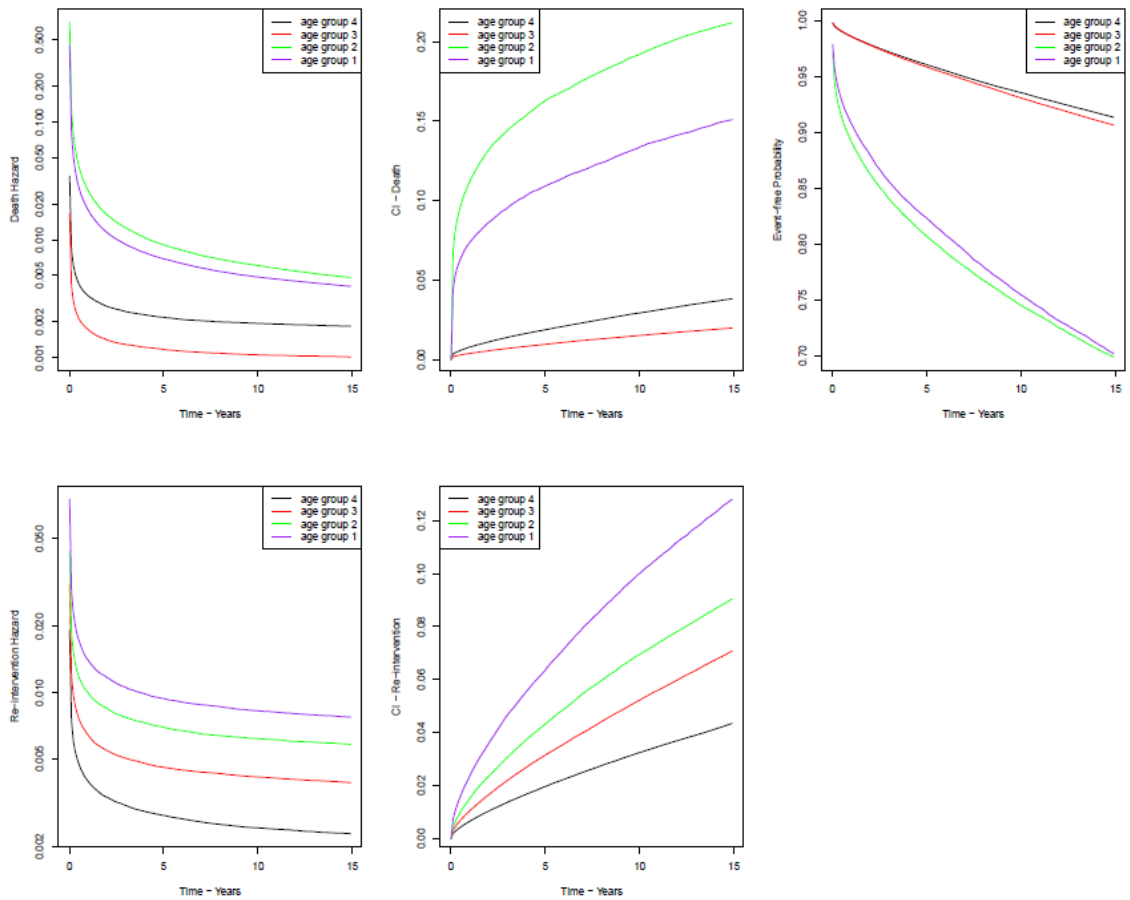


Figure 2

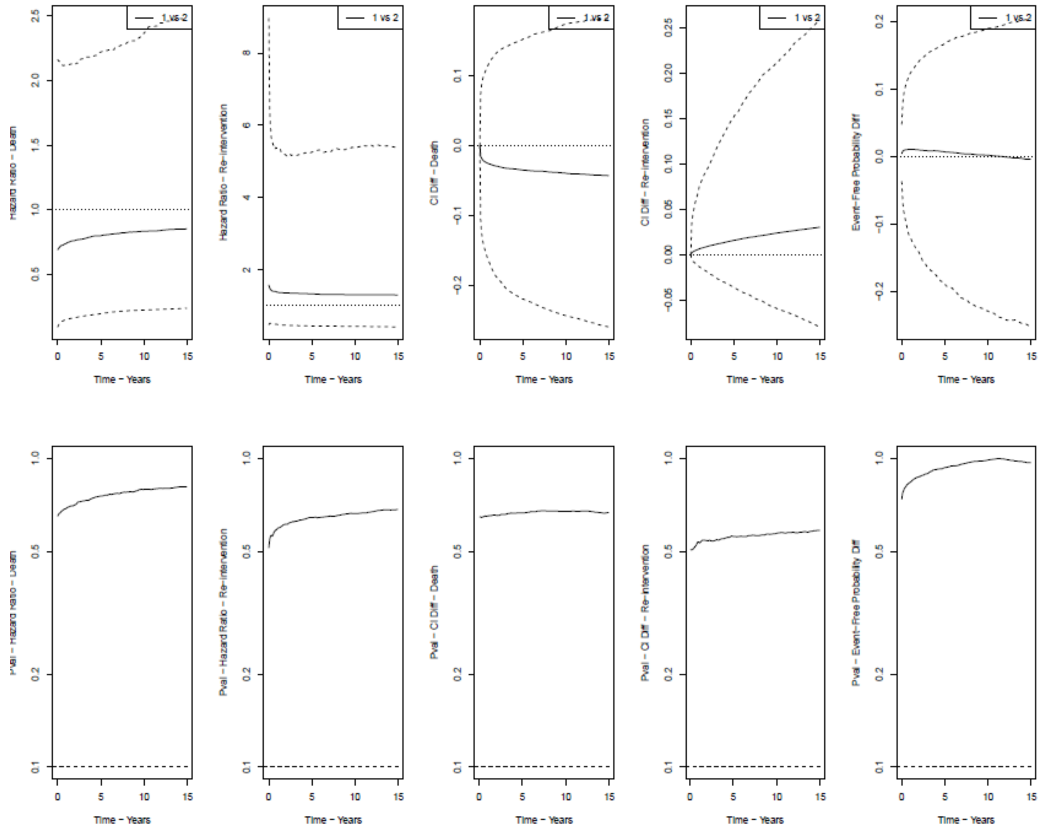



Figure 3

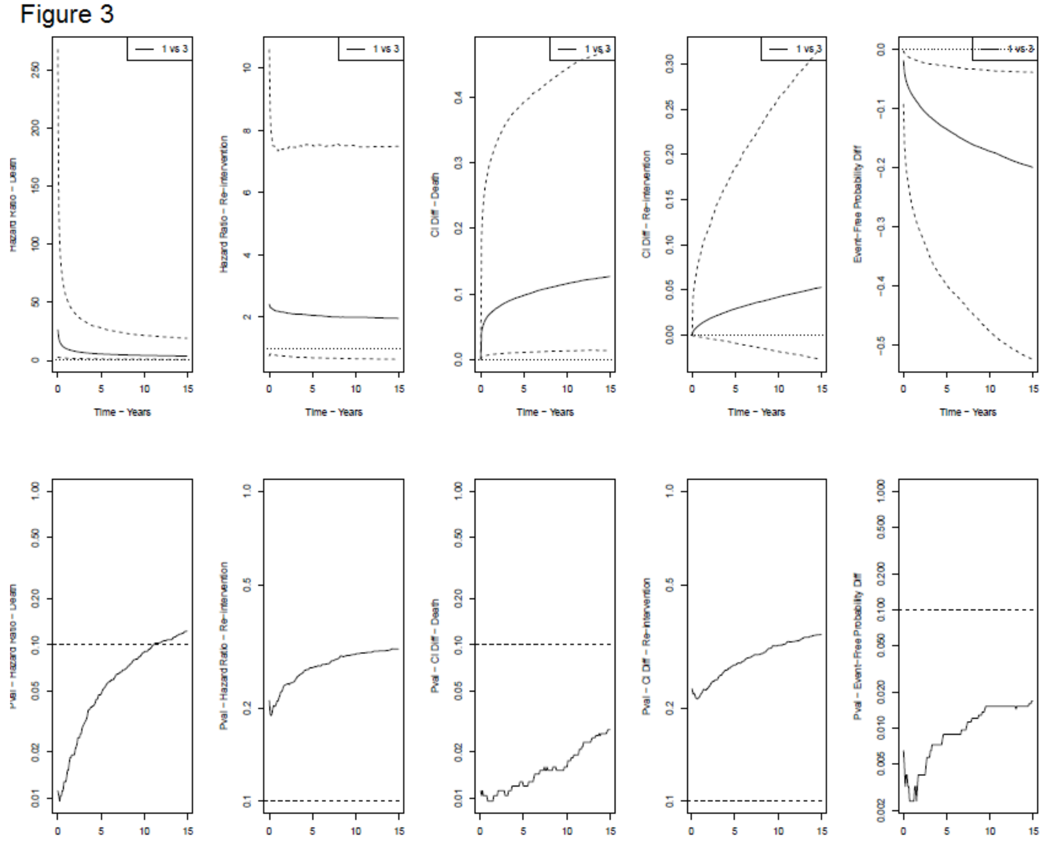


Figure 4

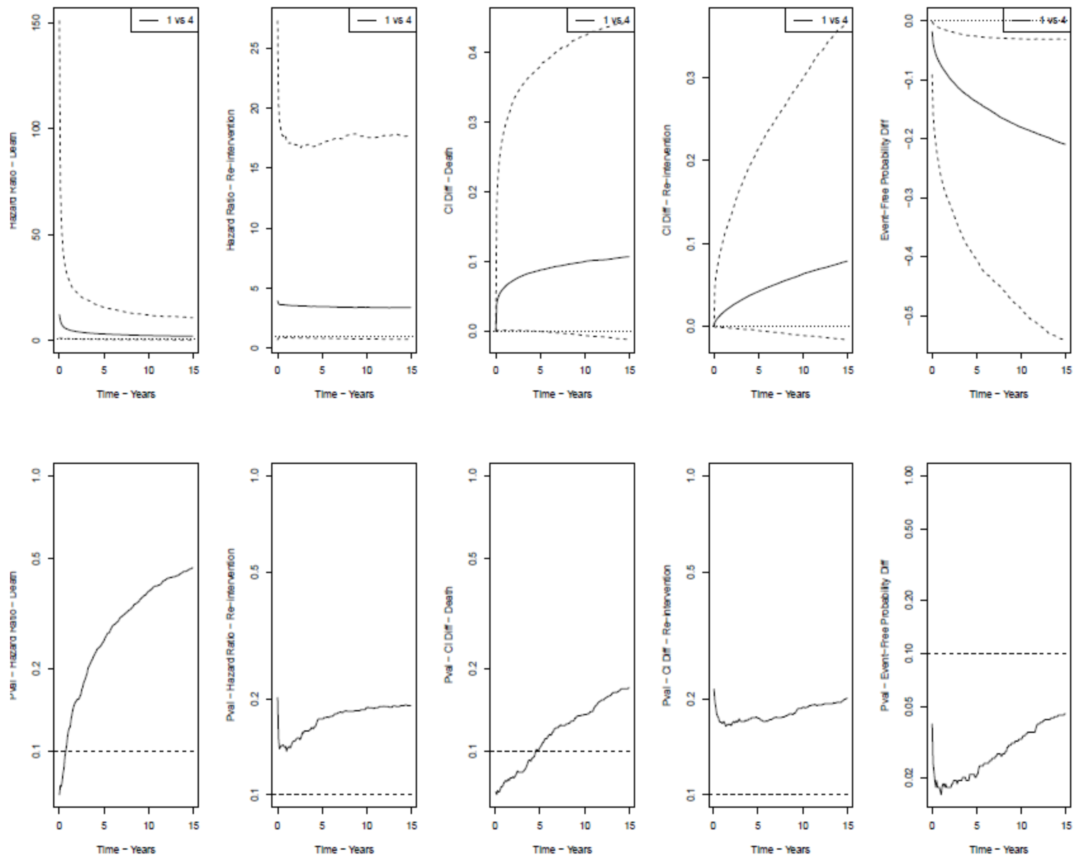



Figure 5

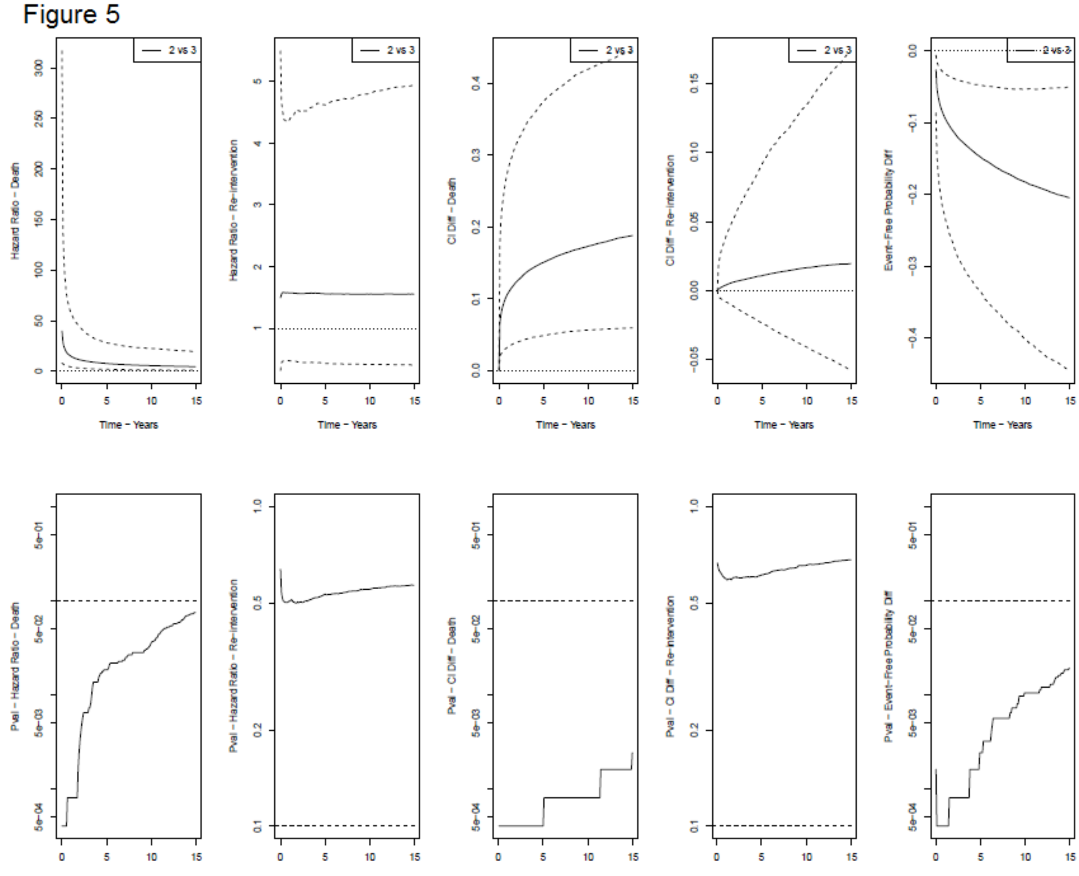


Figure 6

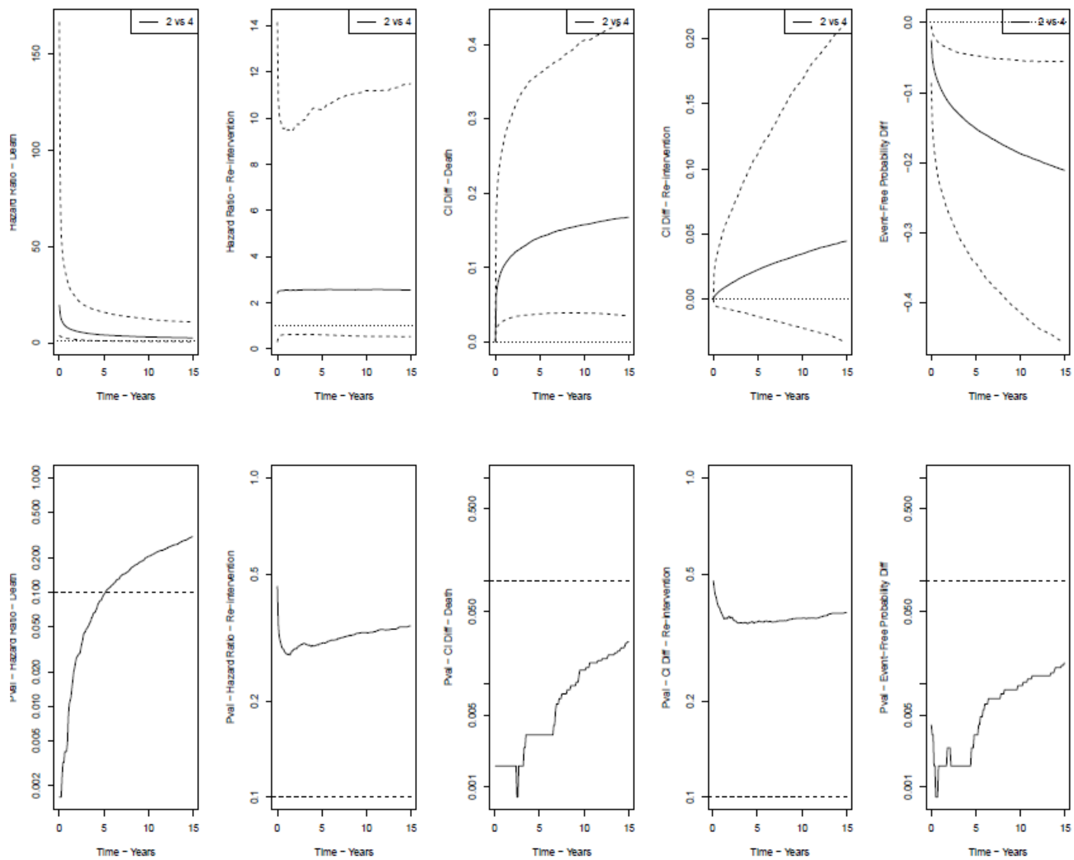
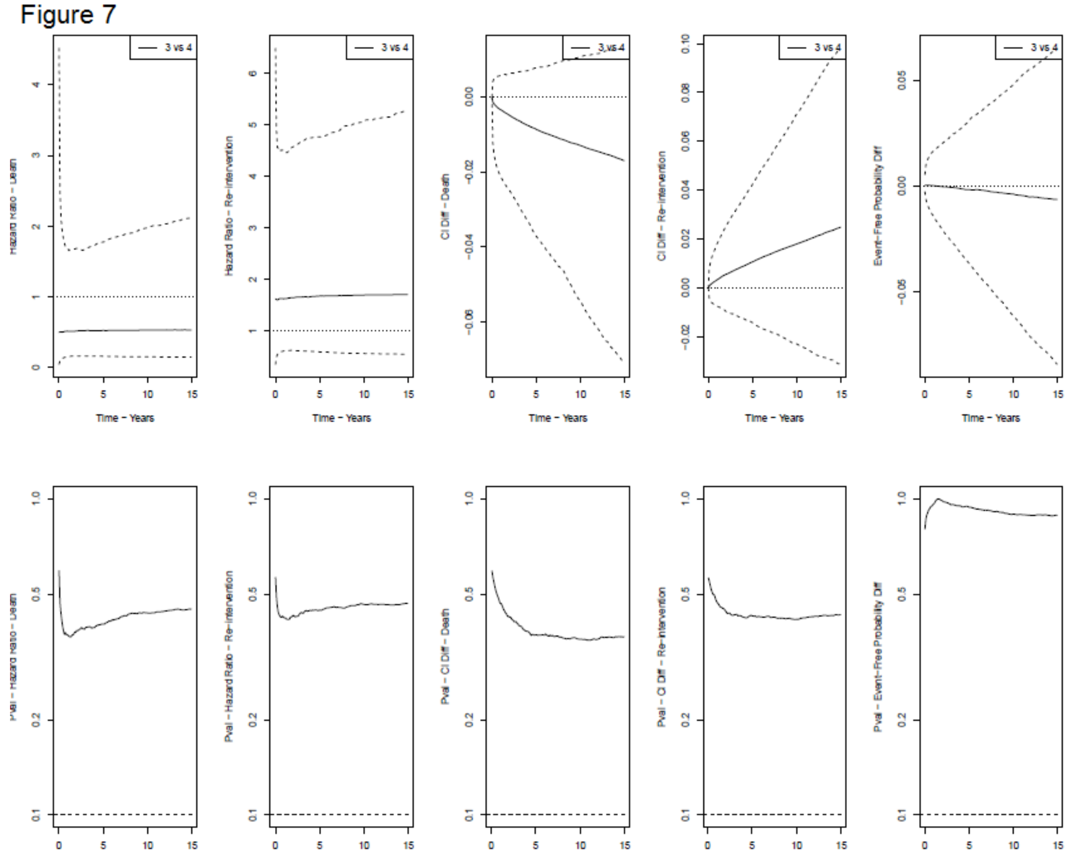



Figure 7



**APPENDIX D**

Plots detailing the impact of the aortic disease type in mortality and aortic reintervention for the Ross procedure, showing hazard, cumulative incidence and event free probability for all four groups (Figure 1) and hazard ratio and cumulative incidence difference with their estimated p values in two-by-two comparisons (Figures 2-7).

Figure 1

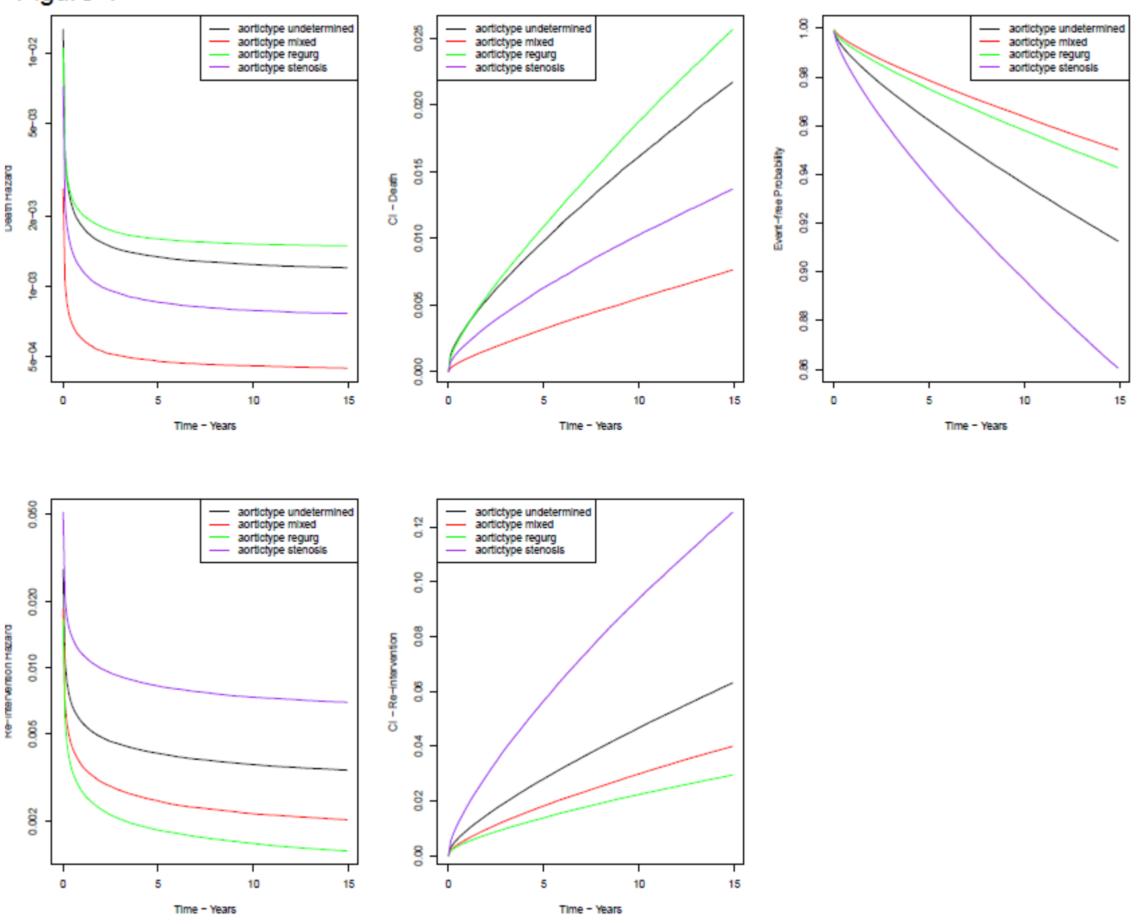


Figure 2

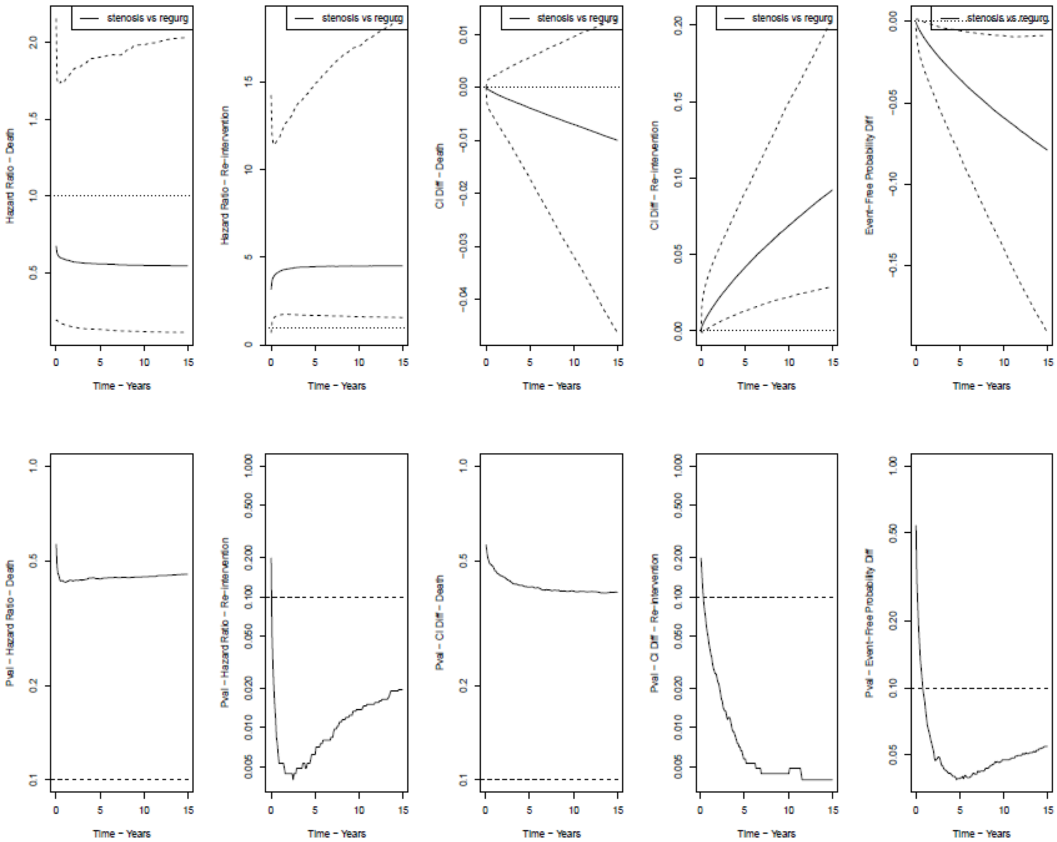



Figure 3

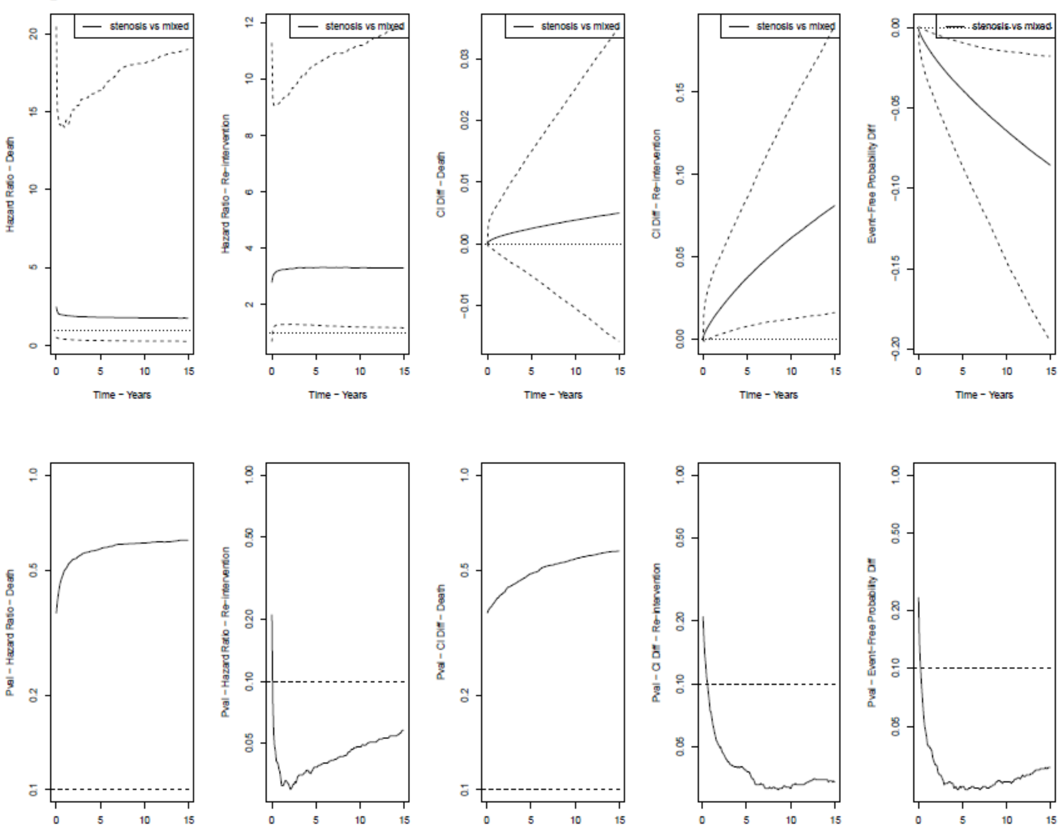


Figure 4

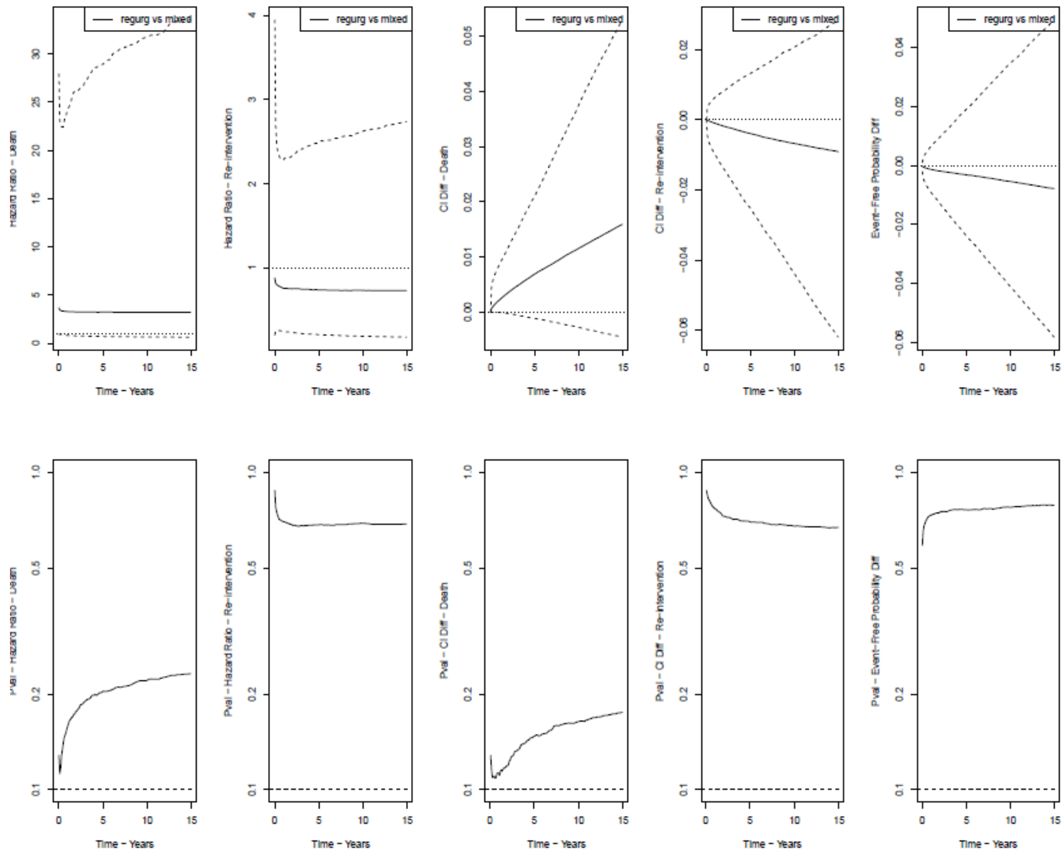
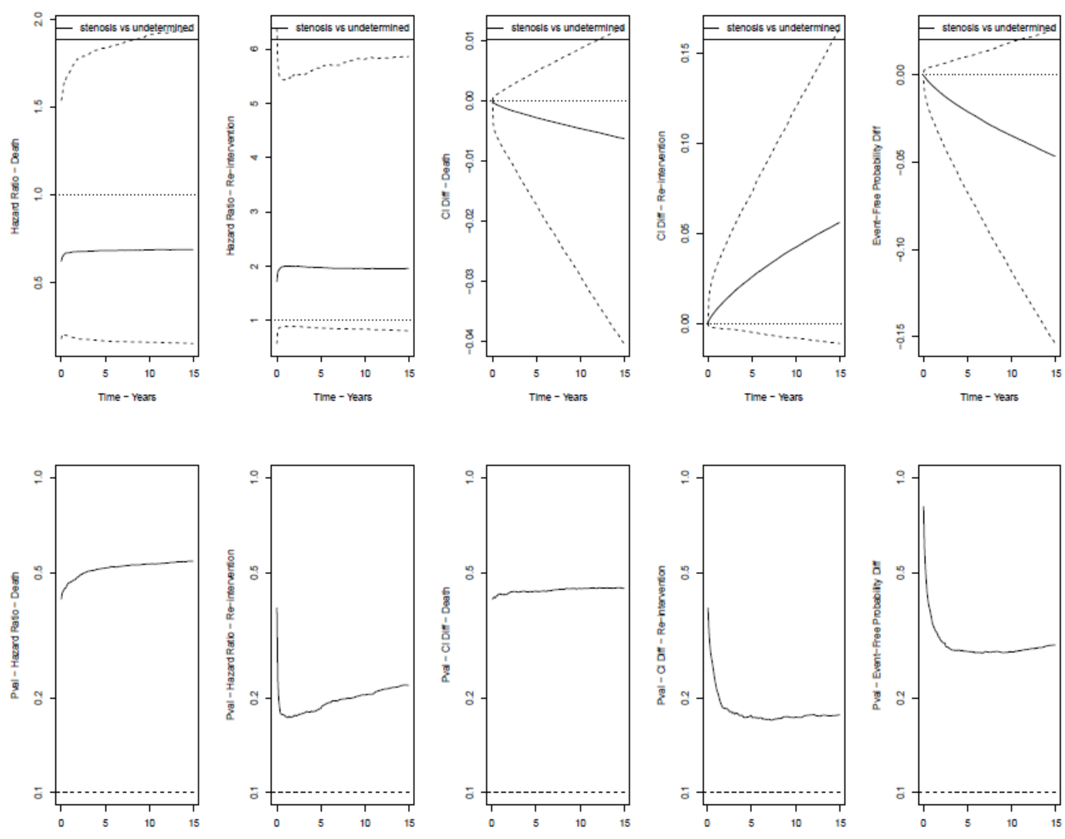



Figure 5



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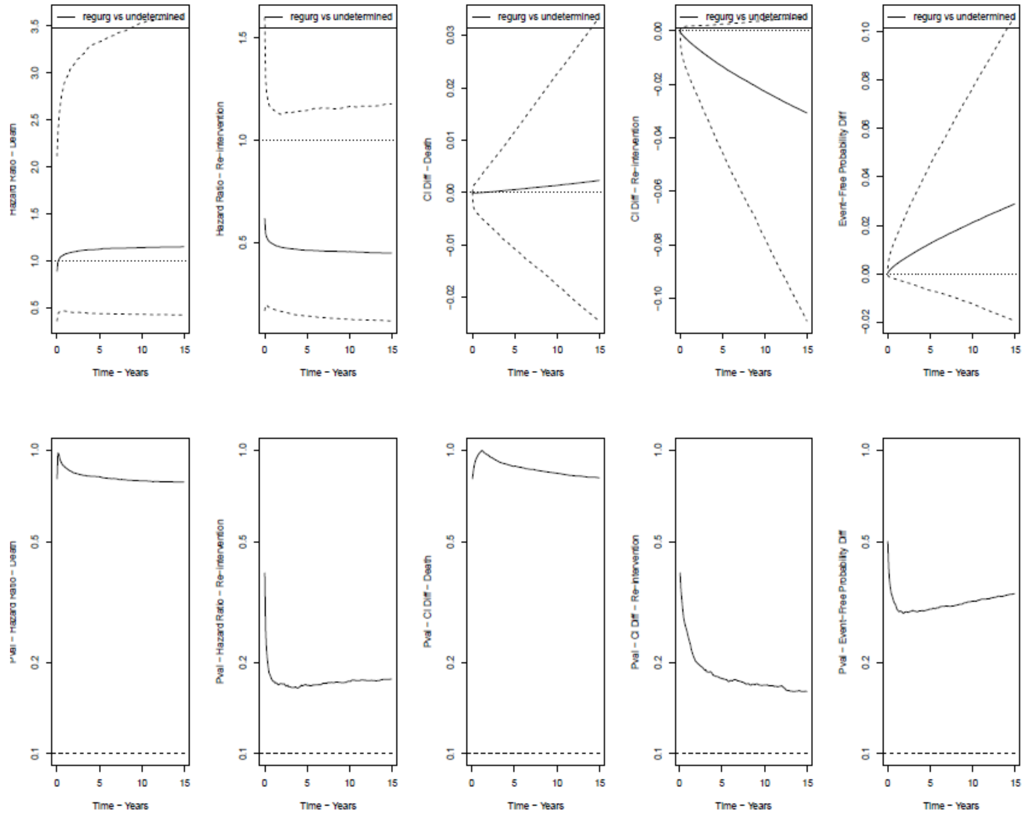


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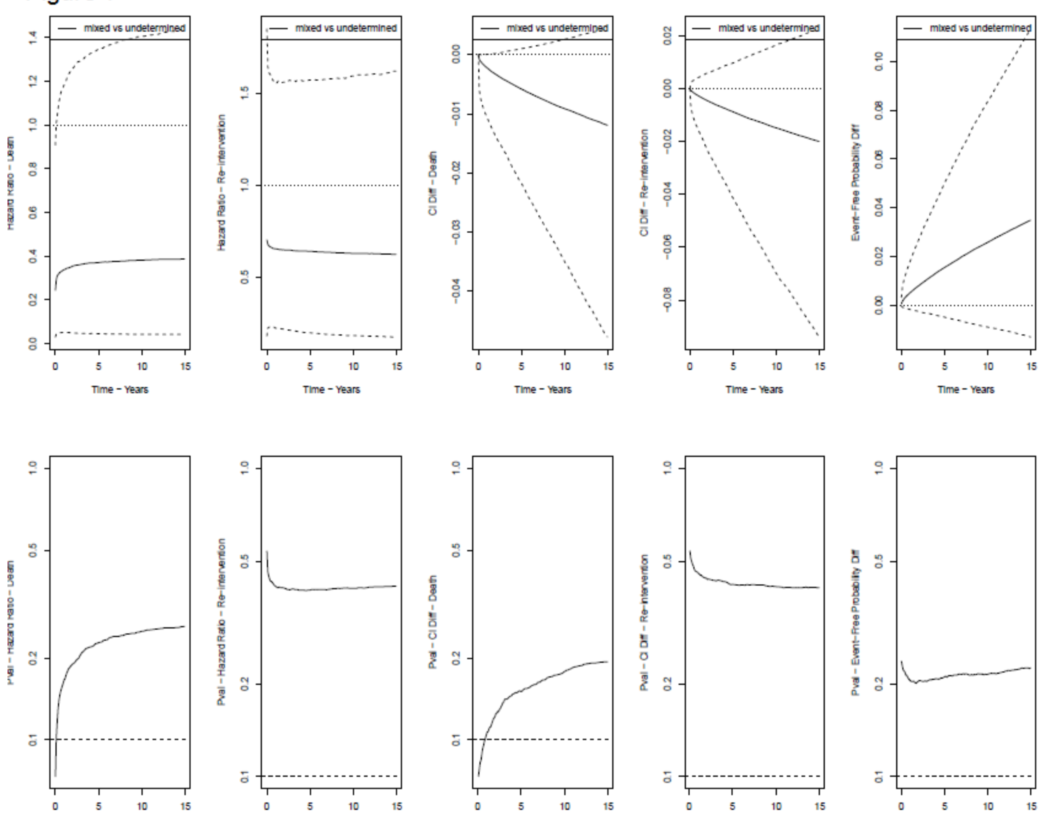
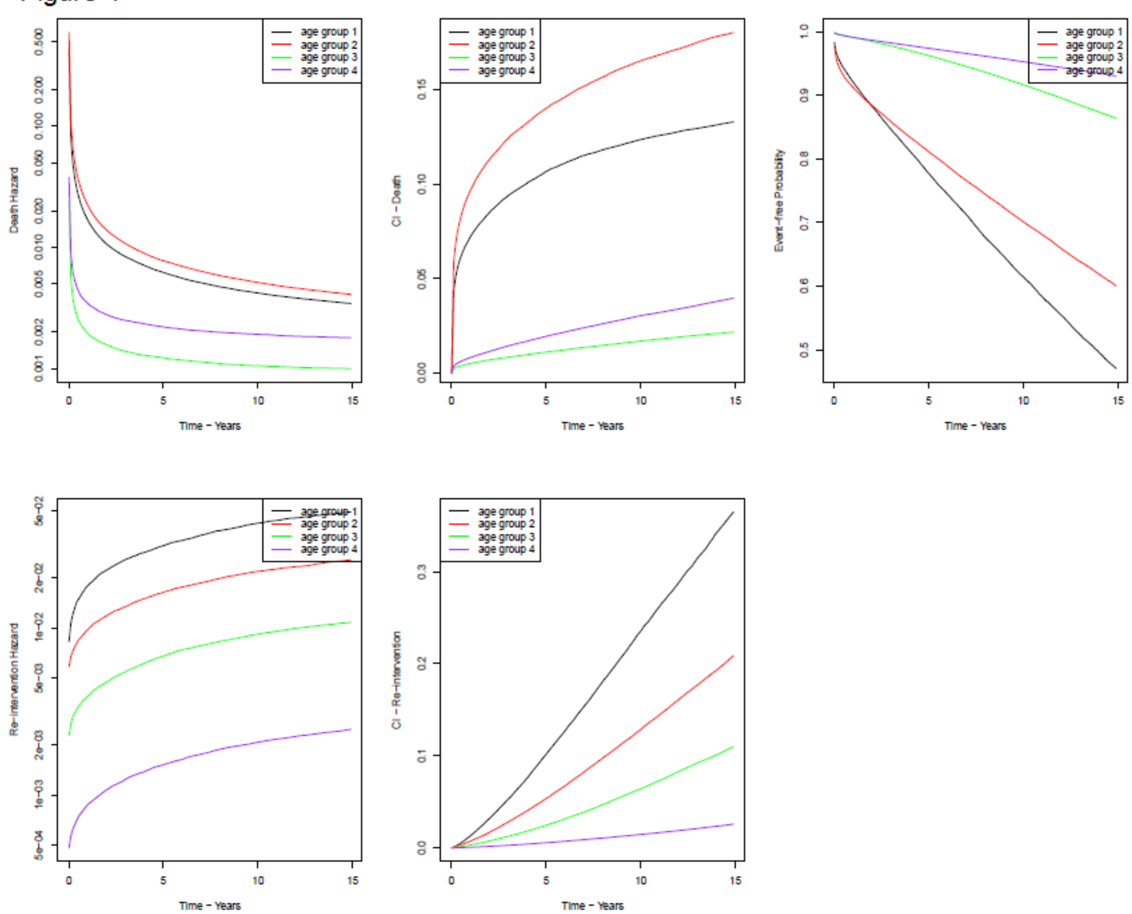


**APPENDIX E**

Plots detailing the impact of the aortic disease type in mortality and pulmonary reintervention for the Ross procedure, showing hazard, cumulative incidence and event free probability for all four groups (Figure 1) and hazard ratio and cumulative incidence difference with their estimated p values in two-by-two comparisons (Figures 2-7). Age groups are as follows: 1 – neonates, 2 – infants, 3 – children, 4 – young adults.

Figure 1



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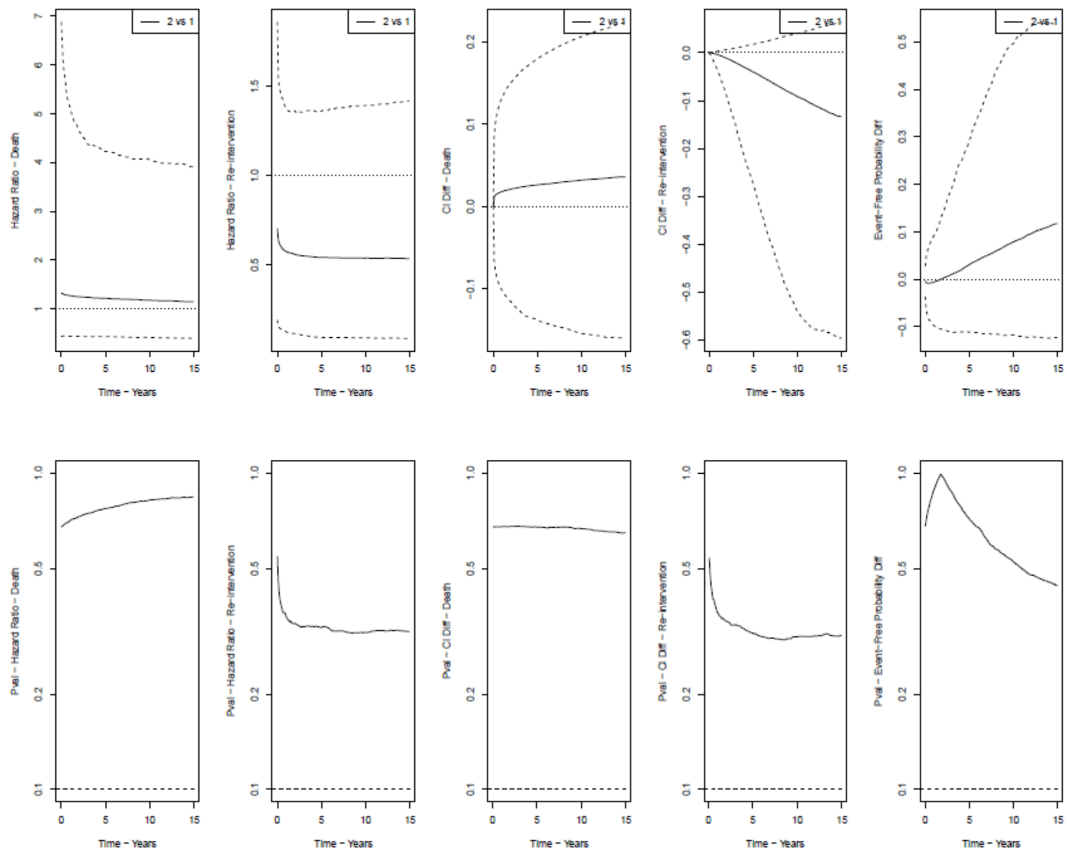


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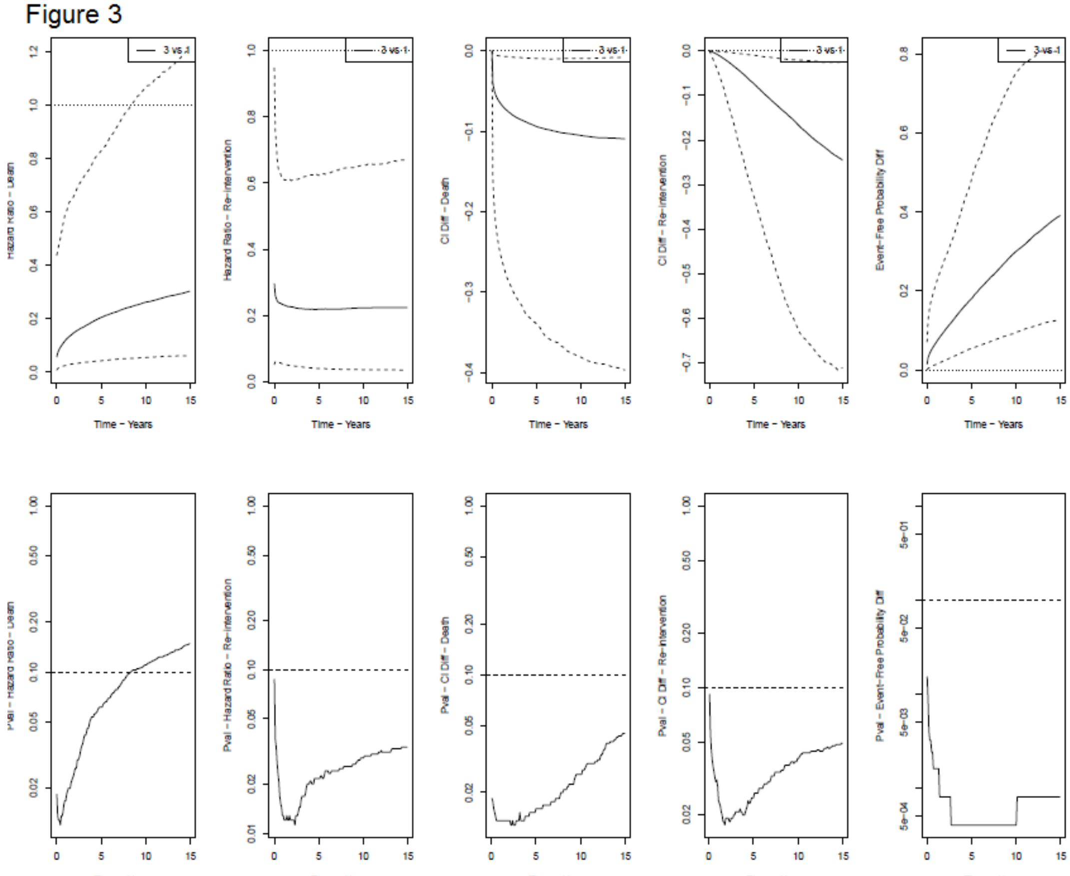

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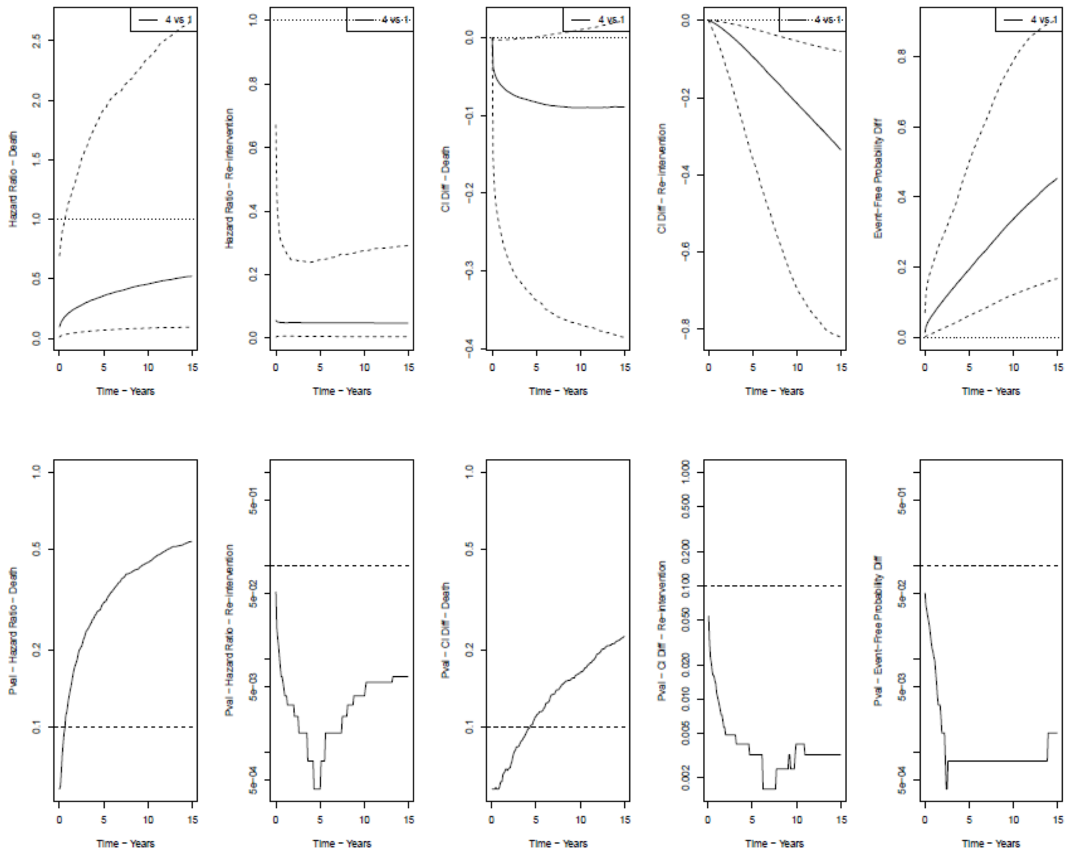


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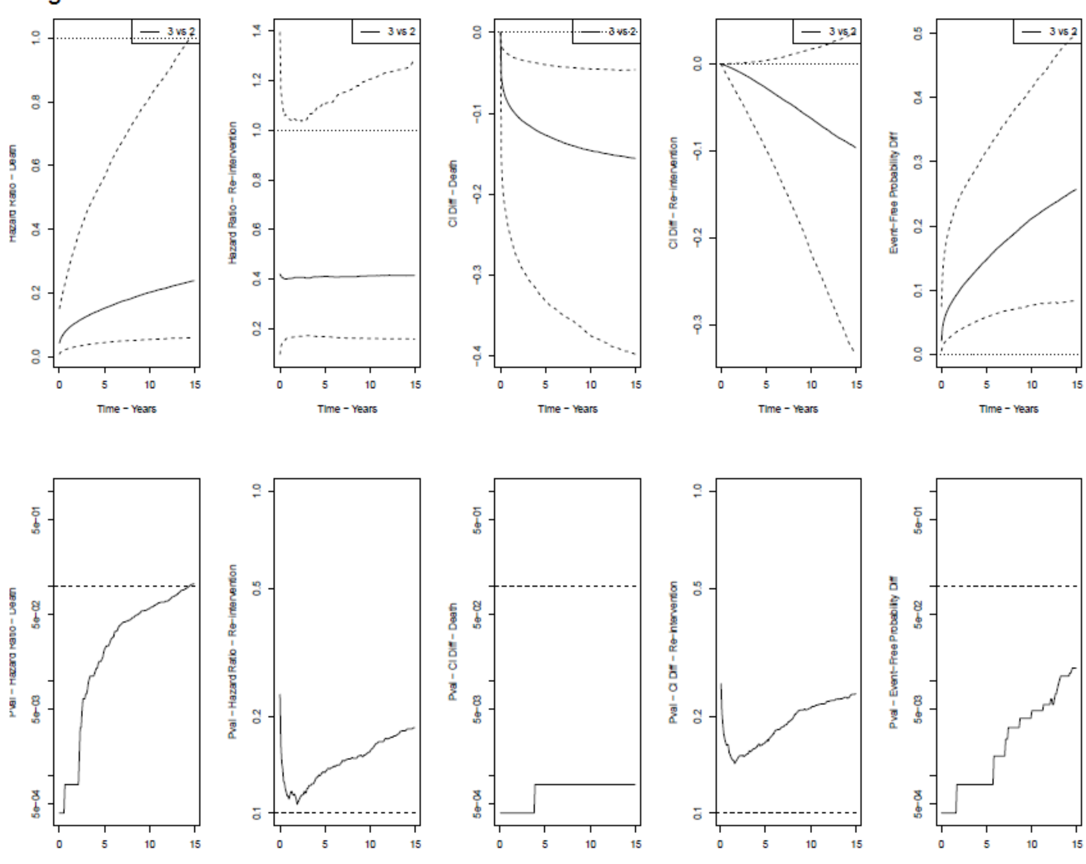

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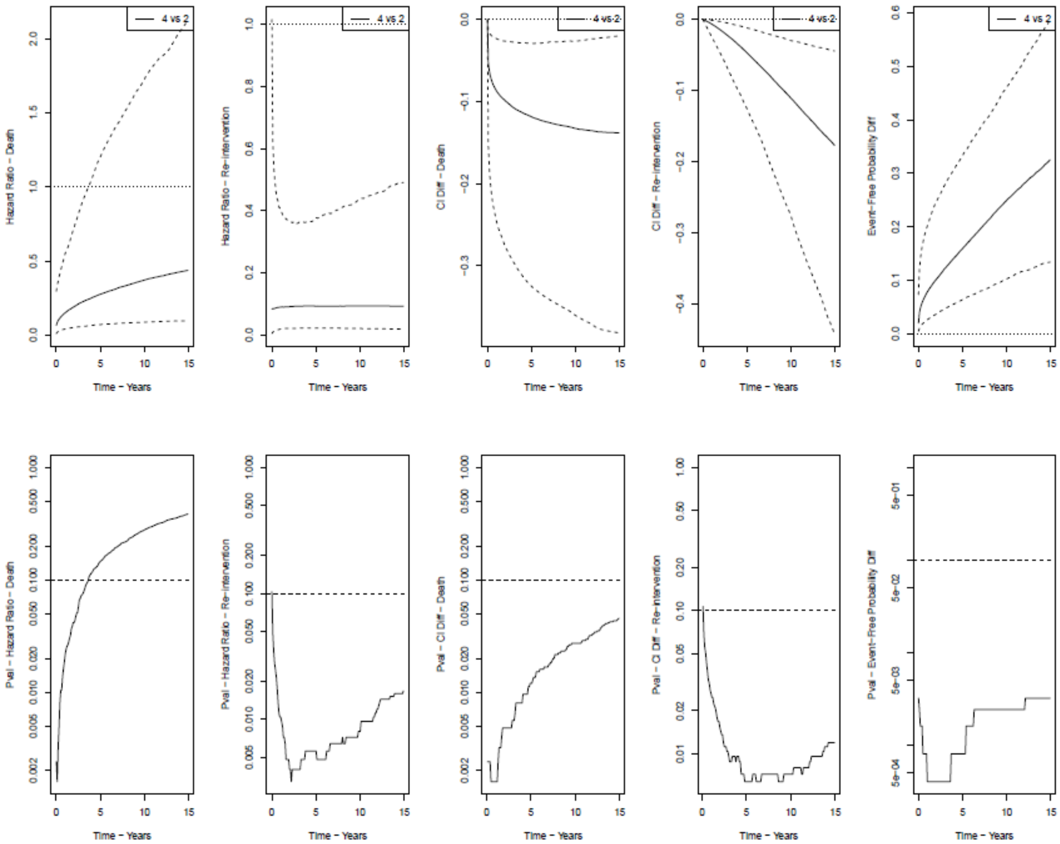


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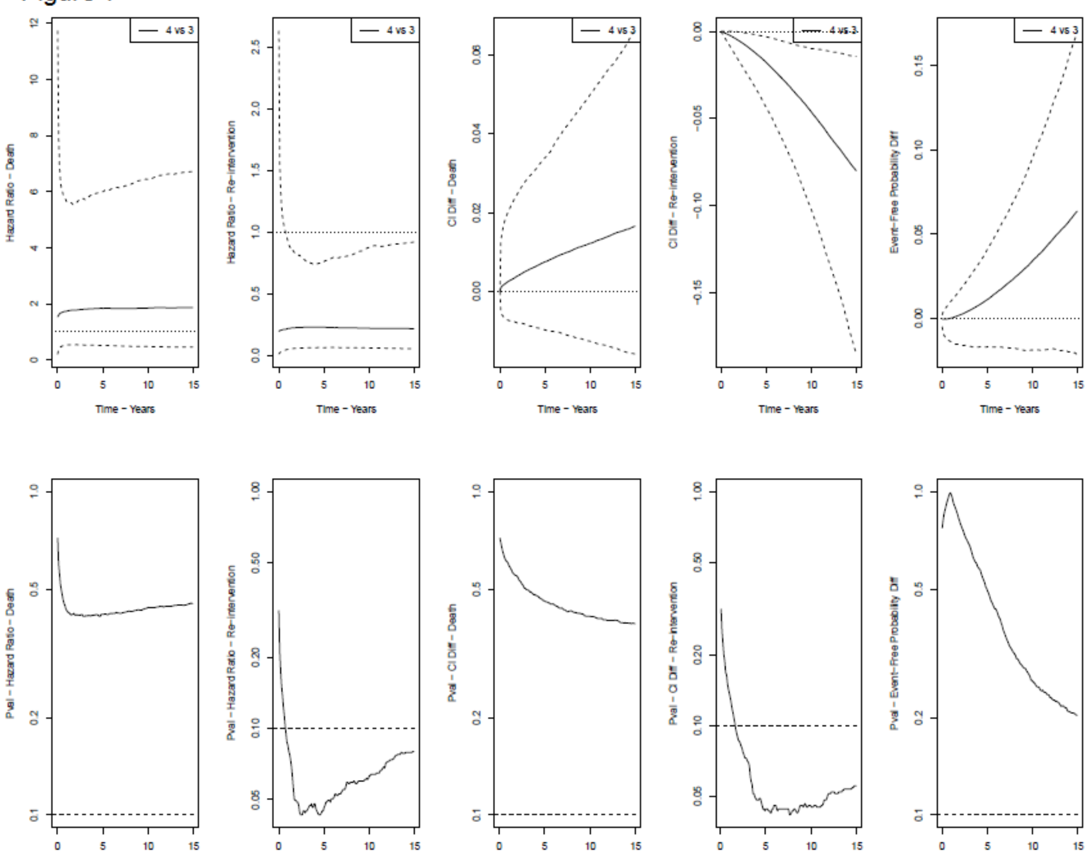


**APPENDIX F**

Plots detailing the impact of the age group in mortality and reintervention for the Mechanical AVR procedure, showing hazard, cumulative incidence and event free probability for all four groups (Figure 1) and hazard ratio and cumulative incidence difference with their estimated p values in the two-by-two comparison (Figures 2). Age groups are as follows: 3 – children, 4 – young adults.

Figure 1

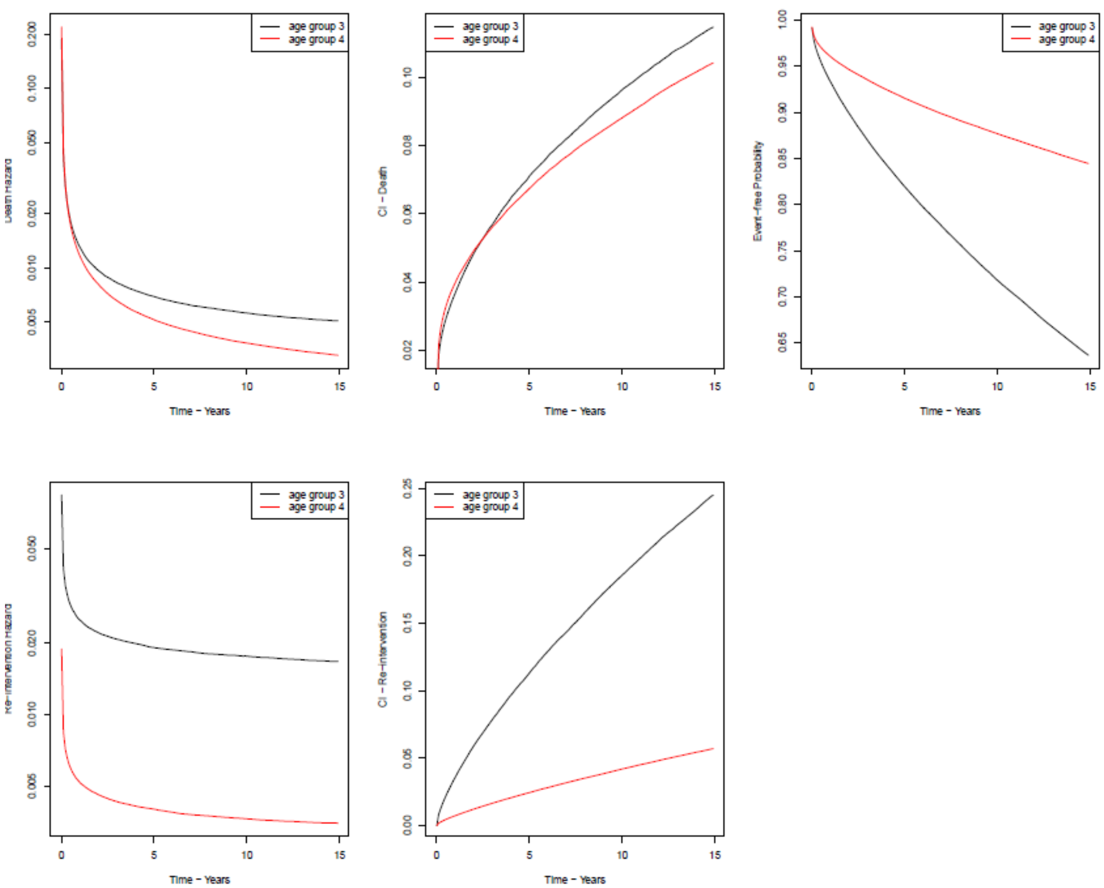
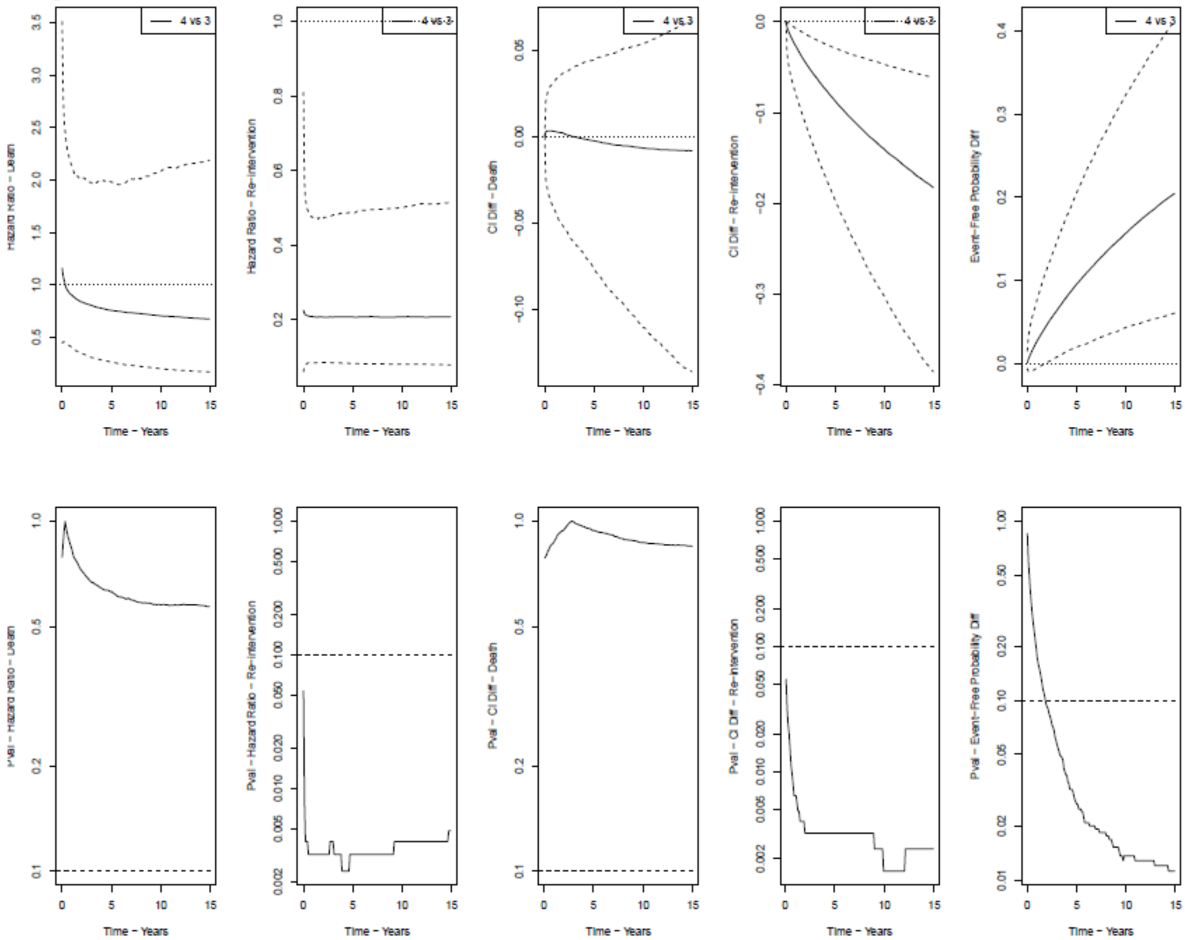


Figure 2



4 vs 3
Hazard Ratio – Death
Hazard Ratio – Re-Intervention
CI Diff – Death
CI Diff – Re-Intervention
Event-Free Probability Diff
Pval – Hazard Ratio – Death
Pval – Hazard Ratio – Re-Intervention
Pval – CI Diff – Death
Pval – CI Diff – Re-Intervention
Pval – Event-Free Probability Diff
Time – Years

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Article entitled: Aortic valve replacement in children and young adults: results from a national database

Manuscript number: JACC012016-0249N

Corresponding Author: Dr. Dorobanru

Corresponding author's printed name: Dan-Mihai Dorobanru

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Manuscript number: JACC012016-0249N

Corresponding Author: Dr. Dorobanru

Corresponding author's printed name: Massimo caputo

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